Sedation of Acute Behavioural Disturbance

A thesis submitted to the

Faculty of Health, School of Medicine and Public Health

University of Newcastle

For the degree of Doctor of Philosophy

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December 2014

Table of Contents

CHAPTER 9: Summation

Declaration

Statement of Originality

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968. Unless an embargo has been approved for a determined period.

Signed_____Dated_____

Leonie Anne Calver

Statement of Authorship

I hereby certify that this thesis is in the form of a series of six published papers of which I am the first author and one unpublished publication. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean, attesting to my contribution to the joint publications.

Signed_____ Dated_____

Leonie Anne Calver

Signed_____ Dated_____

Faculty Assistant Dean (Research Training)

Acknowledgements

Steve, Thank you. For always insisting that I finish this PhD by giving me the option to give up anytime.

Lucas, Bear, Scott and Ashlee, For never having a clue what I was doing but proud of me anyway.

Mum and Dad, Support always. Thanks for always asking how things were going even if I was negative each time.

Geoff, As daunting as it was to be under your supervision it ensured my commitment to the PhD and made me stronger.

Colin, Your contribution was enormous both in terms of professional and personal support. You gave me weeks of your time in ensuring success of this project.

Michael, together with the nurses from the Emergency Department at the Calvary Mater. I relied on your acceptance of the project and thrived on the feedback and enthusiasm. Thank you.

Vincent, An ally very much needed and your assistance appreciated.

Sedation of Acute Behavioural Disturbance

The pharmacological treatment of patients with acute behavioural disturbance (ABD) is difficult and there is little consensus of best clinical practise, which is often based on anecdote and historical practice. Multiple doses of medication and combination therapy are common and often leads to higher total doses being administered or rapid development of tolerance making sedation difficult. The choice of agent remains controversial, but recent studies indicate that droperidol is as effective as benzodiazepines. However, the cardiac safety of droperidol has been questioned. The goal of this thesis was to investigate the benefit of using a standardised sedation protocol with a simple assessment tool for reporting agitation and sedation and used a single agent droperidol for sedation. This included studying ABD in a large cohort of emergency department patients, including a subgroup of elderly patients, and acute mental health patients. The principle findings of the thesis were;

1. The sedation-agitation tool is a simple, rapid and useful measure of level of agitation/sedation in patients with ABD.
2. In a pilot study intravenous dexmedetomidine for difficult to sedate patients with ABD was not safe in the emergency department.
3. In a cohort of 46 patients who had continuous holtor monitoring following droperidol for ABD, QT prolongation was detected in four patients and there was little evidence to support droperidol being the cause.
4. Droperidol was effective for sedation in most elderly patients with ABD and adverse effects were uncommon. An initial 5mg dose appears prudent with the expectation that many will require another.
5. In a cohort of over 1000 emergency department patients with ABD, droperidol effectively sedated over 90% with one or two doses, there were no arrhythmias and only 1% had an abnormal QT, supporting the safety of high dose droperidol.
6. In acute mental health patients large initial doses of sedation were used for ABD in over 50%, and additional sedation was rare. Higher dose sedation didn't result in more rapid or effective sedation but was associated with adverse effects.
7. A controlled trial of droperidol versus haloperidol in a psychiatric intensive care unit found both equally effective for sedation of patients with ABD.

LIST OF PUBLICATIONS

- Calver L, Stokes BJ, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. EMERGENCY MEDICINE AUSTRALASIA 23(6):732-740 2011
- Calver L, Isbister GK. Dexmedetomidine in the emergency department: Assessing safety and effectiveness in difficult-to-sedate acute behavioural disturbance. EMERGENCY MEDICINE JOURNAL 29:915-918 2012
- Calver L, Isbister GK. High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY 77(5):880-886 01 May 2014
- Calver L, Isbister GK. Parenteral sedation of elderly patients with acute behavioral disturbance in the ED. AMERICAN JOURNAL OF EMERGENCY MEDICINE 31(6):970-973 01 Jun 2013
- Calver L, Drinkwater V, Isbister GK. A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health unit. BMC PSYCHIATRY 13:225 Sep 2013
- Calver L, Drinkwater V, Page C, Gupta R, Isbister GK, Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. BRITISH JOURNAL OF PSYCHIATRY Nov 2014
- Calver L, Page C, Downes M, Chan B, Kinnear F, Wheatley L, Spain D, Isbister GK. The safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department. ANNALS of EMERGENCY MEDICINE 2015

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OVERVIEW

Aims

The aim of this thesis is to investigate the management of Acute Behaviour Disturbance (ABD) in different health care settings focussing on the safety of a standardised sedation protocol utilising intramuscular droperidol as a single agent. This requires investigation and monitoring of the effectiveness and the safety of a newly developed protocol in a large and diverse patient population.

Methodology:

Most of the thesis was accomplished by collecting data prospectively from a cohort of patients with ABD in the emergency department (ED) of six hospitals. Within this cohort a number of smaller nested trials to answer specific research questions was conducted. Patients with ABD in the ED given droperidol had clinical details recorded. Data sheets and protocols developed by our study group previously were altered and introduced as part of the hospital's medical records. This ensured accurate data collection for analysis.

Step 1: The effectiveness and safety study: Following the completion of the initial randomised controlled trial of droperidol verses midazolam (DORM) the findings were incorporated into a protocol for the management of ABD . This protocol was introduced into six metropolitan and regional emergency departments and the data collected. The effectiveness of droperidol for the management of ABD was assessed by the time to sedation using a tool to map the level of agitation and the safety of droperidol was assessed by the proportion of adverse events . This included using both standard 12-lead recordings and digital 12-lead holter recordings and regular vital signs monitoring.

Step 2: Sub-sets from the effectiveness and safety study were extracted to investigate difficult to sedate patients and the effects of droperidol on the elderly.

Step 3: To provide findings of investigations of droperidol when used in the mental health care setting.

The broad aim of this project is to have evidence to support the hypothesis that a structured pharmacological protocol using droperidol as the first line sedative medication is a safe and effective approach for ABD and is generalisable to a number of patient populations.

To fulfil these aims, the proposed PhD study program consists of the following 7 main study areas:

1. Evaluation of a scoring system for assessing level of agitation/sedation.
2. A prospective study of difficult to sedate patients using dexmedetomidine.
3. A retrospective analysis of the elderly patients given droperidol for ABD.
4. A retrospective audit of sedation of ABD in the psychiatric intensive care unit.
5. Randomised controlled trial of haloperidol (previous standard care) versus droperidol in the sedation of ABD in Pyschiatric Intensive Care Unit.
6. Investigation of the effects of droperidol on the QT interval using holter recordings.
7. A multi-site prospective observational study of the structured protocol of droperidol use for ABD emergency departments (DORM II).

Outcomes:

Establishing the most effective and safest drug for the sedation of violent and acutely disturbed patients has huge implications for the care of these patients in multiple healthcare settings. This thesis provides findings that intramuscular droperidol is effective for initial sedation, and suggests re-dosing strategies for patients not sedated with an initial dose. The thesis provides comprehensive electrocardiogram data on the cardiac effects of droperidol and the development of an evidence based clinical guideline. The study results enabled a clinical guideline which is evidence-based to be implemented which may be implemented in a varietyof healthcare settings.

Link to Publications

1. **Sedation Assessment Tool to score acute behavioural disturbance in the emergency**
   Calver L, Stokes BJ, Isbister GK. EMERGENCY MEDICINE AUSTRALASIA. 23(6):732-740 2011

After an extensive literature review we found there was not an applicable tool to measure the level of aggression and depth of sedation designed specifically for the emergency department. We needed a tool which is easy to understand, quick to score from a distance and did not involve the participation from the patient. A summary of current tools used are summarized in Table 1 (page 46) of the SAT publication and a description of their features and applicability is stated. To address the short comings of current tools the Sedation Assessment Tool (SAT) was developed to meet our primary and secondary outcomes of the studies to follow. The evaluations of the SAT showed the usefulness and benefits of using a tool to assess the level of aggression and sedation. The original DORM randomized controlled trial (RCT) of Droperidol verses Midazolam for acute behaviour disturbance illustrated the need for a data collection form to meet the needs of the emergency department and the trial's outcome measures. One of the secondary outcomes was effectiveness of sedation, which was measured as the time to sedation. The data sheet used included a scale called Altered Mental Status Score (AMSS) designed by Martel et al and was very effective in gaining the information required for the RCT. The results from the score were used to extend the study into the next phase. However the tool used to score the patient had some features which were not practical and sections of the tool were not being used or recorded. The tool required alteration to make it simpler whilst providing a sound assessment of the level of aggression and depth of sedation. In the paper we provided a plot to compare the changes with the original AMSS over time to ensure the alterations of the tool did not affect prediction of the need to give additional sedation. The necessity for the newly developed tool to be evaluated and published was to ensure a credible tool to score the level of aggression/sedation could be used as outcomes in further studies.. These outcomes required a score to establish the initial level of agitation to identify the need for sedation as well as a score to provide evidence of the effectiveness and time to sedation.. It also provided a sound means to prompt the need for additional sedation which is an important secondary outcome. To ensure the tool was practical for use in the emergency department the time it took for staff to score a patient and the inter-rater reliability were tested and reported favourably. .

2. **Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult to sedate acute behavioural disturbance**
   Calver L, Isbister GK. EMERGENCY MEDICINE JOURNAL. 29:915-918 2012

   In difficult to sedate patients the need to explore other drugs for the sedation of acute behaviour disturbance was highlighted due to the lack of options which were safe and economical. Difficult to sedate patients were defined as those who failed multiple attempts to sedate them and required alternative strategies to manage them. A small number of patients were identified as difficult to sedate after the administration of droperidol 10mg followed by an additional dose of 10 mg but these patients remained problematic. As a last resort using aneasthetic agents such as propofol were sometimes the only alternative which is associated with considerable risk and cost. The use of dexmedetomidine for sedation has been extensively studied in the settings of intensive care unit and the operating theatre but not explored in the emergency department for the management of acute behavioural disturbance. In an attempt to resolve this dilemma of how to safely sedate these patients in the emergency department a pilot study was extended from the DORM II safety and effectiveness study already established. Dexmedetomidine proved to be initially effective in sedating most of the thirteen patients in the study however the sedation was not sustained and higher doses were required. Dexmedetomidine provides light sedation therefore the noise in the emergency department was problematic and impacted on the effectiveness. The larger doses needed to sustain sedation resulted in an increased rate of complications. Monitoring the effects and titration of the dexmedetomidine was resource burning and required intervention for maintenance of cardio-vascular stability. The study was discontinued on the grounds of an unbalanced risk /benefit ratio. The study provided valuable information on the safety and effectiveness of a drug being specific to particular settings only. This pilot study was important to this thesis because it explored an area of management which is yet to be resolved. Dexmedetomide had the potential to be of benefit in this very high risk cohort and it had previously not been trialled in the emergency department setting for ABD.

3. **High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings**

   Calver L, Isbister GK. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY. 77(5):880-886 01 May 2014

The cardiac risk of droperidol in doses for sedation of acute behavioural disturbance has not been investigated before. After decades of safe use Droperidol was issued a black box warning due to concerns regarding its cardiac safety. This was primarily due to non-peer reviewed spontaneous reports which included flawed evidence and has resulted in a restriction and often withdrawal of its use for the treatment of ABD. The reports that droperidol causes QT prolongation were based on

varied and outdated methods of measurement and did not consider other contributing factors and comorbidities. The controversy over the best QT interval measurement technique, the most accurate rate correction formula, and the likely-hood of developing an arrhythmia after drug administration adds to the confusion of how to assess the risk of some drugs. This study employed expensive and not readily available monitoring equipment which required special training research time to analyse the recordings. It involved using a continuous 12-lead recording to detect any change of the QT interval. Cardiac monitoring was commenced following the minimum dose of droperidol10mg and up to a maximum of 40 mg which is reflects the doses given in current clinical practice. This paper included key information on the co-morbidities and contributing factors that possibly could cause QT prolongation and describes the method of measurement to help determine the associated risk. The findings give insight into the importance of including influences that can change length of the QT interval, and explains the importance of not using the QT measurement as an isolated sign of a drug related effect.

4.Parenteral sedation of elderly patients with acute behavioural disturbance in the emergency department

Calver L, Isbister GK. AMERICAN JOURNAL OF EMERGENCY MEDICINE. 31(6):970-973 01 Jun 2013

Determining the most appropriate drug to manage acute behavioural disturbance in the elderly remains a challenge today. Elderly frequently present to the emergency department in a confused state and can become increasingly distressed in the noisy and unfamiliar environment. If sedation is required treatment is complicated by multiple co-morbidities, poly-pharmacy and impaired organ function that makes it difficult to predict their pharmaco-dynamic response. The damaged reputation of droperidol from the black box warning prompted much uncertainty as to the appropriateness of its use in this vulnerable group. All sedation used for acute behavioural disturbance carries inherent risk and this risk/benefit need to be weighed specifically in the patients over the age of 65 years. New generation antipsychotics have recently been used for this purpose yet have a limited effect. Alternatively midazolam is unpredictable and associated with adverse effects. Therefore a prospective observational study was needed to report the safety and effectiveness of droperidol which provides information of the effect, doses required and frequency of adverse effects. All patients over the age of 65years administered with droperidol for ABD were included in the paper . The proportion of patients requiring re-sedation highlighted the need for rapid sedation only to be used as an initial emergency measure to avoid harm, or enable an examination while a management plan can be implemented. The conclusion of recommending half doses initially with an expectation that another half dose may be required for effective sedation was an important finding of the paper.

5. **A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health unit.**
Calver L, Drinkwater V, Isbister GK. BMC PSYCHIATRY. 13:6 pages 18 Sep 2013

This paper was designed primarily to test the generalisability of droperidol for ABD. In the mental healthcare setting little consensus exists as to what is the safest and most effective drug and dose to use regardless of numerous clinical practice guidelines. Mental health units have exposure to acute behavioural disturbance on a regular basis. In the past droperidol was a mainstay for the management of ABD but was replaced by haloperidol following the black box warning. The local mental health care institution had an increased interest in droperidol since the regular use in the emergency department and offered an opportunity to investigate a potential role in the treatment of acute behavioural disturbance in the psychiatric acute care setting. The goal to determine the baseline of current practice within the institution prior to commencing a randomized control trial produced interesting findings. The treatment of ABD proved difficult to ascertain as the details and outcomes of the sedation were not well documented. Therefore a form was introduced into the psychiatric intensive care unit to track each episode of acute behaviour disturbance when parenteral sedation was given. The form was not prescriptive and the treatment for ABD remained clinicians choice. The purpose of the form was to familiarize the staff in using a tool to monitor the time to sedation and track any adverse drug related effects and use of additional sedation. This brought about a change in clinical practice which included recording vital signs and documenting the effects of the drugs used. This study found large doses of antipsychotics and benzodiazepines were used both as monotherapy and in combination with no significant gain in the reducing the time to sedation. The doses given require close observation and monitoring of vital signs, which was incorporated into the form which for the purposes of the study, but since have remained standard clinical practice. The results of the study highlighted the need for a structured protocol and questioned the necessity of administering double doses based on no substantial evidence.

6. A randomized controlled trial of haloperidol verses droperidol for sedation of aggressive behaviour in mental health Calver L , Drinkwater V, Page C, Gupta R, Isbister GK, BRITISH JOURNAL OF PSYCHIATRY. 2014

Haloperidol is the most commonly used drug recommended in the current guidelines in the mental healthcare setting for acute behavioural disturbance. With an increased use of droperidol locally the decision of which drug to use in the mentally disturbed patient was controversial. The introduction of a randomised controlled trial into this setting provided the opportunity to test if droperidol was equally effective in patients who had a mental illness as it has proven to be in patients who are

intoxicated or psycho-stimulated in the emergency department setting. The sedation of the undifferentiated ABD is a key factor for the development of a protocol. Haloperidol is reputedly less sedating than droperidol therefore the potential to provide an option which had this advantage was worth exploring. There was also a question as to whether regular use of antipsychotics may have a blunting effect of the sedative qualities of droperidol. The results from the RCT proved neither of these hypothesis were true and both study drugs were equally effective. There was a large proportion of eligible patients who were excluded from the study due to clinicians preference not to include them. These patients had the same baseline demographics and agitation scores as those recruited to the randomised controlled trial and were given different doses and combinations. The outcomes of time to sedation and adverse effects for this group not recruited were equal to the study patients, indicating that alternative drugs and doses to haloperidol or droperidol 10 mg had no benefit. Notably both studies in the mental health care settings report a very small number of patients receiving additional sedation even though a proportion did not a achieve sedation within the time designated. The importance of this paper to the thesis is that it reinforces not only the effectiveness of droperidol for ABD in a different health care setting, it also adds weight to the need for a set protocol with clear guidelines can be effective regardless of the underlying etiology of the ABD.

7.The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioural Disturbance in the Emergency Department

Calver L, Page C, Downes M, Chan B, Kinnear F, Wheatley L, Spain D, Isbister GK.ANNALS of EMERGENCY MEDICINE. 2014

To challenge the criticism and address the concerns of cardiac toxicity of droperidol, a large scale multi-centre safety study was needed. The numbers needed to power this study required a dedicated group of emergency department clinicians to commit to assist in implementing and supervising and promoting the observational study within their departments. This study is the culmination of years of identifying patients to be sedated with droperidol who were then monitored as per the protocol and collecting the faxed data sheets and entering them into the data base. Much of the information entered did not fit within the study criteria due to the dangerous nature of these episodes and reluctance of staff to interact with these difficult to deal with patients by obtaining an ECG. Many data sheets provided information relevant to the effectiveness outcomes of the study only or the cardiac safety of the study only. To get the time to sedation plus an electrocardiograph within the two hour period was a challenge to the staff within a busy emergency department. The total number of patients who were sedated with droperidol during this four year period was remarkable and yet hundreds more received droperidol within the study sites and were not recruited. This is an indication of the difficulties associated with managing this complex patient group. The sample size of over 1000 with ECGs

within the two hour post droperidol time-frame for the safety study and time to sedation recorded for effectiveness was achieved over a four and a half year period. The primary outcome of the study showed a very small proportion of patients who had QT prolongation following droperidol and the small proportion of adverse effects was an important finding . The ability to track these patients and identify other probable attributable causes was gained from previous studies within this thesis. This study provides the important information to add to the already existing body of studies dedicated to management of ABD. To help resolve the uncertainty of which drug, dose, route, requirement additional sedation, expected time of sedation and likelihood of adverse effects improves the care to the patient and removes the chaos and risk associated with acute behavioural disturbance.

List of Additional publications

- Calver L, Downes MA, Isbister GK. Assessment of QT prolongation in high-dose droperidol administration using continuous 12-lead holter recording. 2011 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, Dubrovnik, Croatia, 24 May 2011 - 27 May 2011. Clinical Toxicology. Informa Healthcare, New York, NY. 49: 203-204. 2011 (Conference)
- Calver L, Page BC, Downes M, Chan B, Isbister GK. Droperidol for sedation of acute behavioural disturbance. Society for Academic Emergency Medicine Annual Meeting 2012, Chicago, 09 May 2012 - 12 May 2012. Academic Emergency Medicine. Blackwell Publishing, Hoboken, NJ. 19: S365. 2012 (Conference)
- Calver L, Page BC, Downes M, Chan B, Isbister GK. Safety of droperidol for sedation and acute behavioural disturbance. Society for Academic Emergency Medicine Annual Meeting 2012, Chicago, 09 May 2012 - 12 May 2012. Academic Emergency Medicine. Blackwell Publishing, Hoboken, NJ. 19: S370. 2012 (Conference)
- Calver Leonie Anne. Sedation for Acute Behavioural Disturbance in the Emergency Department intravenous or intramuscular, droperidol or midazolam-The DORM study. ICEM 2010 International Conference on Emergency Medicine. Singapore (pp339) June 2010 (Conference)
- Calver L Intramuscular droperidol vs midazolam for violence and acute behavioural disturbance in the emergency department. Critical Care Conference Hunter New England NSW Health (pp 11)April 2010 (Conference)
- Calver L. Sedation for acute behavioural disturbance in the emergency department; intravenous or intramuscular, droperidol or midazolam-The DORM study. 2nd Improving Delivery of Emergency Care Conference. Gold Coast QL govt. August 2010 (Conference)
- Isbister GK, Calver L. Managing aggressive and violent patients. Australian Prescriber 34(6):National Prescribing Service 2011 (Journal article)

Co-author Statement

Manuscript: Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult to sedate acute behavioural disturbance. Emergency Medicine Australasia. 23(6):732-740. 2011

Co-author: Geoffrey K Isbister

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, the review of the monitoring of the effectiveness, the data collection and contributed to the writing of the paper.

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Manuscript: High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. British Journal of Clinical Pharmacology. 77(5):880-886 May 2014

Co-author: Geoffrey K Isbister

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Co-author: Barrie Stokes

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Manuscript: A randomized controlled trial of haloperidol verses droperidol for sedation of aggressive behaviour in acute mental health. British Journal of Psychiatry. Nov 2014.

Co-author: Colin Page

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Co-author: Rahul Gupta

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Manuscript: Parenteral sedation of elderly patients with acute behavioural disturbance in the ED. American Journal of Emergency Medicine. 31(6):970-973. June 2013

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Co-author: Betty Chan

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Co-author: Fran Kinnear

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Co-author Statement

Manuscript: The safety and effectiveness of droperidol for acute behavioural disturbance in the emergency department 2015

Co-author: Geoffrey K Isbister

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Co-author Statement

Manuscript: A multi-site prospective safety study of droperidol for acute behavioural disturbance in the emergency department

Co-author: Luke Wheatley

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, the recruitment of the sites, ethics applications, implementation of the study, data collection and input and writing of the paper.

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Co-author Statement

Manuscript: A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health care unit. BMC Psychiatry 13:225 Sep 2013

Co-author: Geoffrey K Isbister

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, the collation, review and analysis of the data and writing of the paper.

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Co-author Statement

Manuscript: A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health care unit. BMC Psychiatry 13:225 Sep. 2013

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Literature Review

Sedation of acute behavioural disturbance

Introduction:

Acute behavioural disturbance (ABD) is a common occurrence in emergency departments (ED) and mental health institutions and often requires the use of drugs for the purpose of sedation. Violence and verbal and physical aggression can pose a safety risk to the patients and staff in the health care environment. The factors most commonly implicated in these episodes are alcohol intoxication, psycho-stimulant toxicity, deliberate self-harm, drug overdose and mental illness[1, 2].The optimal goal in the management of patients with ABD is to ensure safety and to allow assessment and treatment to proceed. This is best achieved by containing potentially dangerous behaviour with focussed interventions[3-7]. An important component of these interventions is effective sedation. There are a number of factors which complicate safe and effective sedation. These include consideration of which drug or combination of drugs to use, the dose that is adequate yet minimal, the route of administration. Added to this is the different healthcare settings which provide different challenges such as monitoring the effects of the drugs which can compromise the safety of the patient. Other factors are the complications which arise from rapid sedation which include over-sedation and other drug related adverse effects. The most common adverse effects are respiratory and cardiac complications. The means of monitoring, measuring and avoiding the implications of these risks from the effects of drugs used for sedation remains controversial. Patients who do respond to the recommended drugs and doses within the expected timeframe are problematic and are classed as "difficult to sedate" Difficult to sedate patients provide another challenge as to how to proceed with further attempts safely with avoidance of harm. These factors have largely been ignored in the context of acute behavioural disturbance and the aim of this thesis is to address these concerns. This includes investigating the safety of a drug removed after years of proven effectiveness in ABD and exploring the prospect of improving management of ABD by implementing directed prescriptive protocols. The need to better manage this difficult and often dangerous patient group is the purpose of this body of work. Currently, medications used to control violent and aggressive behaviour disturbance has been based on anecdotal evidence and /or historical clinical practise with little or no supporting evidence based outcomes or guidelines. My goal is to address these issues and provide better support for both the patients and healthcare workers.

This review of the literature will include definitions of the acute behavioural disturbance followed by factors contributing to and influencing it. Review of past and current guidelines, sedative drugs, adverse effects, controversies and identify the gaps between the literature and clinical practise.

1.0 Definition of Acute Behavioural Disturbance :

ABD is expressed in many forms and the source of the behaviour stems from agitation which is a complex state. Lindermayer et al describe agitation as a constellation of comparatively unrelated behaviours that pose a risk to the safety of the patient or health care worker,

impedes the process of care giving or impairs a person's function[8]. The complexity of the factors and mechanisms which drive and control emotion are not well defined. They can be partially explained by the fact that agitation and aggressive behaviour appear to be linked to many receptor types including dopaminergic, serotenergic, noradrenergic, and sometimes glutamatergic-GABAergic systems [8]. Acute behaviour disturbance can be expressed in many forms of behaviour. The Clinical Practise guideline for Management of Acute Behaviour disturbance in Hunter New England Health defines ABD as where a patient shouts, threatens, gesticulates violently, spitting, threatening harm to others or deliberate or unintentional self-harm, throwing items, shaping to fight, punching walls, charging at or physically assaulting staff or other patients[3, 6].It is recognised that behavioural emergencies will continue to be a problem because of their tendency to occur outside the usual context of healthcare[9]. As patients usually seek help and agree to accept the care provided to them the healthcare professional often struggles with the concept of the patient being obstructive and violent when trying to provide care and act in their best interests. The lack of capacity for the patient to consent to care often results in restricting their movement in the form of physical restraint. This patient management without consent is covered under the Duty of Care in tort law. Duty of Care is the legal responsibility to look after others so that they do not incur harm[10]

1.1 The Incidence of ABD:

ABD is not recognised or classed as an illness and it is a transient acute state. This makes the use of the terms incidence and prevalence difficult but in this context the term incidence will be used as it defines the number of new cases of ABD commencing, during a specified time period in a given population[11]. The frequency of violent episodes is now recognised as a major health priority by the World Health Organisation, the International Council of Nurses and Public Services International. Nonetheless, workplace violence to healthcare workers has continued to rise [12]. With the frequency of presentations of ABD as a proportion of ED presentations increasing over the years, it has reached a level that requires concerted action[13]. Despite this well publicised fact there remains no national or international clinical practise guidelines that clearly direct the management of ABD in the emergency setting[7]. The UK national audit office (2003) noted a 40% increase between 1999 and 2002 in self-reported violence by National Health Service staff[4]. The Australasian College for Emergency Medicine cites a rate of violent incidents to be approximately 3 per 1000 presentations to the emergency departments, and under reporting of violent incidents by health care workers is common[14]. Data published by Downes et al suggest the frequency of these events may be significantly higher than previously quoted in the Australasian ED literature. This study showed a relatively high incidence of approximately 5.5 violent incidents per 1000 patient attendances per annum[1]. This compares with a 12 month prospective survey of security codes studied in Melbourne that quoted an incidence of 3.2 activations per 1000 patient attendances per annum[15]. A ten-fold increase in the number of patients attending the ED with primarily mental health problems has occurred over the past ten years[16]. These figures include those experiencing drug and alcohol abuse. It was also found in a review to explore the relationship of violent/homicidal behaviours and mental illness, that people suffering from serious mental illness are two to fifteen times more likely to report violent behaviour than people with no

mental illness[17-19]. There appears to be a consensus in the literature that the incidence of ABD is worsening in all healthcare areas[13, 18, 20-25]. This highlights the importance of reviewing what management is currently being practised with an aim to improve upon it.

1.2 Causes of ABD

There are a number of underlying causes of acute behavioural disturbance as well as a wide variation in the severity of individual episodes. The causes can be roughly divided into the following;

- Organic: delirium from medical disorders, including substance abuse and other toxidromes
- Psychotic: schizophrenia, mania, bipolar and other mental illness.
- Nonorganic nonpsychotic: personality disorders, acute situational disorder, impulse control disorders[26].

The most common causes in the emergency department tend to be organic in nature and include acute drug and alcohol intoxication, confusion / agitation related to behavioural disorders, or threatening self-harm or poisoning[1, 2]. This is in contrast to the psychiatric admission units where psychosis is the commonest cause followed by psych-stimulant substance abuse[27]. The reason for ABD is multi-factorial and often involves social factors, bad life-style choices and patients are sometimes in police custody[28]. ABD requires early intervention[15] to prevent harm and reduce risk. Despite the aetiology of the aggression it has not been found to predict the response, in studies of treatment of acute agitation [29, 30]. The cause of the ABD is most often not obvious and cannot be investigated until after the ABD is controlled. To obtain a history of events leading up to the ABD is not always possible. Some signs and symptoms such as the smell of alcohol or dilated pupils can give some clues as to the cause of ABD but this is not definitive and many presentations are multifactorial[26]. Many clinicians and guidelines focus on determining the cause of the ABD to differentiate how to treat it. Contrary to this the concept of treating ABD with an undifferentiated diagnosis opposes the cause determining the treatment. It saves valuable time in the emergency and simplifies the choices and streamlines the process [30].

Stimulants:

A common cause of ABD are abuse of psycho-stimulants. Psycho-stimulants such as cocaine, amphetamines and methamphetamines act by increasing central nervous system activity. People who present to the emergency department are those who are naïve to the effects of stimulants or have ingested a greater volume or strength, or indulged in poly-pharmacy. They usually present in states of acute agitation and loss of self-control. In extreme cases this can lead to mental illness and death[31]. The adverse effects on the cardiovascular system from stimulants has been reported decades ago. In 1973 Lipski reported brady-arrhythmias and repolarisation abnormalities in a significant number of drug-dependent individuals[32]. More recently the cardiac effects suffered from stimulant abuse has been well documented and

include diffuse or local coronary artery spasm, hypertension, hypertrophy, QT prolongation, myocarditis, cardiomyopathy, valvular damage, ischemia and infarction[33-35] This has implications for investigating the cardio-toxic effects of sedation for the treatment of ABD as the risk may be pre-existing. The choice of the type of drug to sedate a patient as determined by the diagnosis or reason for presentation remains controversial. An example of this approach is the comparative randomised controlled trial of droperidol verses lorazepam for ABD from methamphetamine abuse which concluded that droperidol produced a more rapid and profound sedation than lorazepam for methamphetamine toxicity and lorazepam is more likely to require repeat dosing than droperidol[36]. Another trial which used drugs specific to the cause of the ABD used dexmedetomidine for cocaine intoxication to counteract the cardiovascular effects in healthy cocaine naïve adults compared to placebo in combination with morphine and benzodiazepines . The benefits of the dexmedetomidine over morphine or benzodiazepines were noted to be better in due to the absence of respiratory depression[37]. Many guidelines specify a different drug regime specific to amphetamine toxicity yet there is no evidence to support this strategy[9].

Alcohol:

The most common cause of ABD in the emergency department setting is from intoxication from alcohol[38, 39]The link between alcohol and violence is irrefutable[40]. The mechanism by which alcohol exerts its effect on the brain remain an enigma[41]. The relationship between the pharmacological effects of alcohol on GABA potentiation and dopaminergic neurons and susceptible individuals are factors which play a role on the levels of aggression[42]. There is a strong association between substance abuse, depression and suicide attempts. It is the disinhibition caused by alcohol that is thought to lower the threshold for attempt or completion of the act of suicide[43]. Commonly patients who have been drinking excessively arrive in the ED via police and/or ambulance as intoxication is often associated with violence and /or trauma. The agitated and intoxicated patient invariably does not want to stay within the healthcare institution as they usually did not present voluntarily. As it is the responsibility of the healthcare staff to prevent the person from leaving, defined as duty of care[10], this conflict together with alcohol dis-inhibition results in ABD. The choice of agent to treat ABD specific to alcohol intoxication has a general consensus limited to not using benzodiazepines [44], yet many guidelines do not differentiate and midazolam remains the first-line option. This poses considerable risk due to the CNS depressant effect of alcohol to cause respiratory compromise. The combination of benzodiazepines and alcohol intoxication causes respiratory depression leading to oxygen desaturation and over-sedation resulting in airway obstruction. Additionally, benzodiazepines should not be first line treatment for intoxication because both benzodiazepines and alcohol potentiate GABA which decrease fear when faced with a threat. Therefore when given together can result in an aggressive response. This dis-inhibition and aggressive response to provocation in patient given benzodiazepines when intoxicated with alcohol is known as paradoxical aggression and is called a dis-inhibitory reaction. This robust link of alcohol and sedatives that bind to GABA are known to increase feelings of hostility, competitiveness and retaliatory behaviour[45]. The alternative agents used for sedation are the

antipsychotic which need to be considered as the better choice when dealing with ABD related to alcohol for the reason of less respiratory compromise and less over-sedation[2]. Also olanzapine and alcohol are not recommended to be used in conjunction with benzodiazepines[46] which further complicates the management.

1.3 Settings of ABD

ABD in Mental Health institutions:

The primary aim of sedation in the acute psychiatric setting is to achieve "rapid tranquilisation" This is defined as light sedation to allow comprehension and to maintain contact with the patient to enable psychiatric assessment[11] .The objective of sedation in the emergency department is to achieve "rousable sleep" as the priorities are to restore calm for a physical examination and investigations to get a diagnosis. The NICE guidelines note that rapid tranquilisation may lead to deep sedation/anaesthesia as any sedation has unpredictable effects[11]. However, the distinction between the objectives are less relevant in the cases of the most severe acute behaviour disturbances where the priority is safety first in both settings. Rousable drowsiness is an appropriate immediate objective for ABD and the drugs used for behavioural emergencies have both tranquilising and sedative effects[47]. This somewhat blurs the boundaries as to what the primary aim of sedation / tranquilisation is within the mental health care setting. It may explain the reason for the agent of choice being haloperidol which has remained the mainstay of conventional antipsychotics use to treat undifferentiated ABD. There is a cross-over of the primary diagnosis in the mental healthcare setting and the emergency department because many patients with mental illness have associated drug and alcohol problems[48]. Often benzodiazepines or a combination of benzodiazepines and antipsychotics are commonly used[29, 49, 50]. It is generally accepted that poly-pharmacy should be avoided and medication doses should be as low as possible to decrease the associated risk of rapid tranquilisation[51]. Literature supports this strategy of combining agents by indicating that lower doses of each component medication are able to be used when combined to lower the adverse effect rate, especially from haloperidol[52]. This strategy in the clinical setting has been questioned in a recent retrospective study of a mental healthcare psychiatric intensive care unit which reported higher doses in combination therapy was prevalent[52].

ABD in the emergency department setting:

Nurses face one of the highest rates of workplace violence[53] and ABD is most prevalent in the emergency departments of hospitals[44, 54] The primary aim of sedation in the emergency department is to reduce the risk to the patient and the staff and to enable diagnosis and treatment. Rousable sleep is ultimately the goal yet deeper sedation can be managed if necessary due to access to airway equipment, drugs and staff expertise. Much literature focuses on the sedation of patients in psychiatric institutions[55] where most patients have psychotic illnesses and the requirement for rapid sedation is less common. This is in contrast to the emergency department where a smaller proportion of patients have a diagnosed mental illness and the more common presentation is a patient with an agitated delirium associated with drug abuse and self-harm. No other area of clinical medicine, including psychiatry, is exposed to such a steady flow of potentially assaultive or destructive patients as is the

emergency department[30]. The environment, observation, and the use of physical restraint are specific to emergency departments and have special requirements in addition to those addressed in psychiatric in-patient settings[11]. Despite the prevalence of ABD within the emergency department setting there is a dearth of clinical practise guidelines to direct the management of this emergency. A recent mail out survey has estimated that only half of emergency departments have local guidelines to refer to[7]. The care is guided by anecdotal evidence and clinicians experience and individual preference[11].

1.4 Severity of ABD

There are varying degrees in the severity of agitation and which needs to be understood before various results from studies can be applied to clinical practise. Many published articles describe management of agitation recommend oral medications as the best measure [20, 56]with no accounting for the resistant patient incapable of compliance to treatment. Patient selection biased of studying less severe ABD is evident in many studies which require written consent and electrocardiographs (ECG) and blood sampling prior to treatment and recruitment to a study [57]. There is doubt as to the need or goal of sedation in trials requiring consent[11] such as the olanzapine trials[58, 59]. Addis et al states there are many randomised controlled trials which rely on sufficiently "well" enough patients to provide this informed consent[60]. This brings into question the severity of agitation. If the patient has the capacity to agree to act in their own best interest by swallowing a tablet, or are rational enough to consent to a trial and/or have the ability to remain immobile for procedures. In the Range of Behavioural Disturbance the term "overt hostility" is used to described the most intense and dangerous ABD in the Expert Consensus Guidelines series [9]. Petit et al describes violence as behaviours used by individuals that intentionally threaten or attempt to or actually inflict harm on others[6]. This definition of violence omits to note the intention to harm to oneself. ABD can occur in patients with the diagnoses that are sub sets of psychiatric disorders[16]. Kalucy et al categorised these to include depressive /affective disorders, mania, psychotic disorders, psychoneurotic and anxiety disorders, suicide and self harm, personality disorders, organic brain syndromes and alcohol and drug misuse or abuse. Given the diversity of clinical entities from which agitation may arise it is not surprising that it is among the most commonly encountered clinical problems in the psychiatric facilities and the emergency services[20]. ABD regardless of the cause is characterised by distinct observable behaviours. The signs and symptoms of a patient who is agitated and potentially violent can be listed on a spectrum of severity and include pacing being least agitated, and violent outcomes consisting of screaming ,cursing, yelling, spitting, biting, throwing objects, hitting or punching self or others, or attacking or assaultive behaviour[6]. Clear inclusion and exclusion criteria are necessary to differentiate between the severity of agitation and therefore the need to treat. In a recent randomised controlled trial of sedation for ABD in the emergency departments in Australia [39], ABD was defined as combative or aggressive patients who were at risk to themselves and others and who were unable to be verbally de-escalated and refused oral or IV medication. Although this is a simplistic approach it provided clear criteria in order to define those patients in need of restraint and/or sedation. An objective way to measure the severity of ABD is by scoring the patient using a set of observable parameters. The many

available tools for scoring patients level of aggression has been reviewed extensively in the Sedation Assessment Tool paper[61] which validates the tool used in the many studies related to ABD.

2.0 Management of ABD introducion:

The management of ABD is considered an emergency. Such emergencies are managed with clinical skill, common sense and possibly medication[62]. Initially, "un-differentiated agitation" is the diagnosis given as the reason for presentation as the patient is most often impossible to assess or diagnose until they are compliant or sedated. The reason for presentation being unknown or provisional at best requires the need both to intervene immediately despite limited data to change course rapidly[3]. A coherent approach by the ED staff to ABD is required to optimize patient and staff outcomes[15].

Management of the mild ABD includes options such as verbal de-escalation and administration of oral sedatives are the first and second line strategies in the treatment of these agitated patients[20, 29, 30, 63, 64]. When these strategies fail clinicians are forced to resort to physical restraint and drugs administered by the parenteral route (intramuscular and intravenous) for rapid sedation. This is the primary focus of this body of work as it is fraught with miss-management and controversy.

The management of the extreme cases of ABD in the most difficult to sedate patients, anaesthetic agents and intubation may be employed which then require critical care facilities. All attempts to avoid this is a priority as it is resource draining and exposes the patient to risks of further complications.

2.1 Restraint Practices

The risk of injury to the patient with ABD is significant as they are not capable of making informed or rational decisions. They may be intent on self-harm or violence toward staff and need to be physically restrained against their will. Physical restraint is the last resort to prevent harm not only to the patient, but to the health care workers and often other patients. Physical restraint is defined as the skilled hands-on immobilisation or the physical restriction of a patient to prevent the patient from harming him/herself or endangering others or to ensure the provision of essential medical treatment[65]. Physical restraint incorporates either manual restraint (personal containment by force) or mechanical restraint (using devices) or seclusion (isolation rooms). Restraint practices reflect institutional practice, rather than being dependent on the patient characteristics[66, 67]. Some emergency departments manually hold patient down until they settle enough to trust they will not harm themselves others or abscond. Whilst others departments restrain the patient long enough to connect the manacles then stand back creating a space between the patient while they settle. Other institutions manually move the patient into a prone position and hold them long enough to administer the injection and then retreat outside the seclusion room and observe the patient remotely. There are disadvantages to all the approaches. In a survey of 116 Australasian emergency departments 87% used manual restraint as a prelude to chemical restraint and a large number used mechanical restraint as well (69%)[7]. Stubbs et al stat that physical interventions should

not be used as a stand- alone intervention to manage aggressive patients[22] and recommends drugs be used simultaneously. In contrast Currier and Trenton make the statement that rapid tranquilisation is an *alternative* to physical restraints often used to manage agitated patients[56], yet they cite Brattaglia's [68] statements regarding the benefits of rapid tranquilisation including the reduction of time in the agitated state, and importantly less time in restraints. Physical restraints may be associated with several complications. The most common is skin injury at the site of the restraint, which may have associated neurovascular damage[26]. Management of patients with ABD is a significant problem for public safety and emergency medical agencies, and death has occurred during restraint of patients[56]. Continued struggling against restraints is recognised as a medical emergency[69] Hick et al reported 5 deaths whilst in restraints due to profound metabolic acidosis which was associated with cardiovascular collapse following exertion in a restrained position. The need for "aggressive sedation" is recommended by Hick et al due to the need to prevent struggling[69]. Experts agree that the goal of the use of medication is to reduce the time of the patient in seclusion but simultaneously introduces potential risks[9, 11].This underpins the importance of sedation being used together with physical restraint.

2.2.Medical and Pharmacological Management

Administering medication for the purpose of rapid sedation is required to expedite assessment of the patient[70] and to protect the patient and staff. Rapid effective sedation is usually the last and often only option for controlling the patients with ABD. Parenteral sedation compared to physical restraint is felt to be more humane and safer for managing combative patients[30, 71].There are a number of choices required once to decision to sedate has been established. These include the type of drug, dose and route of administration. The term *Rapid tranquilisation* is mostly used in the mental health setting and has been described as giving antipsychotic medication to control behavioural disturbance [72]. Rapid tranquilisation is effective across all diagnostic categories, regardless of the aetiology of the aggression [30]. The term *sedation* is not specific to the class of drug used, and the term is more commonly used in the ED setting. However, drug treatment for ABD requires careful consideration of the balance between effective management of symptoms and potential adverse effects. Adverse effects can range from a drop in the oxygen saturation requiring little or no intervention to the need for mechanical ventilation or even death as reported by Michalodimitrakis et al[73]. There is inherent risk associated with any attempt to rapidly sedate a patient with ABD, the most common is respiratory depression, airway compromise and hypotension[74].

Current Guidelines

There is conflict between the demand for evidence based treatment protocols and individual clinical experience[75] consequently there is ongoing controversy about the safest and most effective medications for sedation of violence and acute behavioural disturbance in the ED[76]. Tremendous variability exists in the approach to agitation, both across geographical regions and across providers within regions[56]. A recent Australian mail survey conducted by Chan et al supports the need for standardisation of management of ABD. The most important outcome of the survey was consensus among the responders that the most important

perceived barriers to agitation management included both lack of training and a lack of national Clinical Practise Guidelines[7]. Cannon et al found fewer than half of the EDs in Australia had local guidelines available to clinicians[77].

An Australia survey of 783 responders reported 500 clinicians preferred to use combination therapy although there is limited evidence to support this practise[7]. The Expert Consensus Guidelines Series recommend using combination treatment of a benzodiazepine and antipsychotic for "greater efficacy, onset of action and reduced side effect liability"[3]. The authors note that the literature is inconclusive as to whether the combination treatment actually produces these benefits. The potential benefits of using combination therapy are that half doses of each agent can be used thereby reducing the risk of dose related adverse effects[11]. However a retrospective study of sedation in the acute psychiatric setting reported that combination therapy was usually associated with larger total doses being administered as the dose of each agent was not reduced[52]. The Hunter New England Mental Health Guidelines for Medical intervention in Acute Behavioural Disturbance in Adults 2007 recommends midazolam 2.5-10mg IMI or if contraindicated or ineffective recommends resorting to haloperidol. The NSW Health Reference Guide for Mental Health for Emergency Departments 2009 recommends the intramuscular agent be benzodiazepines (preferred), midazolam or lorazepam the medication to be used, and provide a caution about the risk of respiratory depression[78]. Published surveys support the consensus that these guidelines are not evidenced based and clinical practise is greatly varied. In a mail out survey from the USA of 20 psychiatric emergency departments [50], they found that the of the twenty Medical Director respondents that eleven had a preference for a haloperidol/lorazepam combination(+/- benzotropine), whilst only 4 and 3 respectively preferred droperidol and benzodiazepines (unspecified) for the drug management of aggressive people. Another survey conducted in preparation for a randomised trial, in the psychiatric emergency rooms of Rio de Janeiro in 2001, found that haloperidol /promethezine mixture was most commonly used (83%) for emergency intramuscular sedation of severely agitated/aggressive people[79]. In Australia the most recent survey conducted was that of a cross sectional mail survey of members of the Australian College of Emergency Medicine[80]. The findings were if monotherapy was chosen, respondents preferred midazolam 622/783 (79.4%; 95% CI 76.4-82.2) to manage the ABD scenario where no history was available, followed by haloperidol 47/783 (5.8%; 95% CI 4.3-7.7) and olanzapine 38/783 (4.9%, 95% CI 3.5-6.7). It is clear that since the black box warning against droperidol it is now rarely used or recommended in current guidelines. The Maudsley prescribing guidelines have changed from recommending droperidol in Step 1,2 and 3 for acute disturbed or violent behaviour in 2001[49] to recommending haloperidol as the replacement. This change occurred after the black box warning and has remained the same to date. The swing back to the use of haloperidol is curious in the ED setting given that it has also been issued with a black box warning is less sedating and is known to cause more adverse drug effects[3].

ACEM endorsed clinical practise guideline[14] was the most commonly accessed reference used by Australian ED clinicians[7]. Most recently a clinical practise guideline has recently

been released by the Hunter New England Area Health which advocates the use of droperidol or haloperidol in adult patients in the Mental Health Setting[81] .

Route of parenteral administration – Intramuscular verses Intravenous

Effective sedation is often defined as sedation that is titrated to the point of rousable sleep, but not unconsciousness[63]. Titration is only possible when using the intravenous route (IV). However the intramuscular (IM) route is always used in the mental health setting and more commonly recently in the ED setting. There are advantages and disadvantages of both.

IV route:

Advantages;

- Quicker onset of action
- Smaller initial doses required due to titration

Disadvantages;

- Greater risk of needle stick
- Skill required to insert cannula
- Need to immobilise the patient to obtain intravenous access
- More staff are required to physically immobilise the patient

In highly aggressive patients, titrating intravenous sedation has traditionally been thought to be an effective way to rapidly sedate patients as the onset of action of the drug is faster. While there are advocates of intravenous (IV) medication, the advantages of IV medication have not been convincingly demonstrated [82, 83]. In a study of seven different sites in England recently the authors noted that from the 332 patients all of the parenteral sedation was administered via the IM route. The setting was psychiatric intensive care units and the the authors[75] pointed out the change in practise clearly differing since Pilowsky et al's 1992 study when IV medication was used in more than half of rapid tranquilisation episodes within the same setting[84]. The emergency department survey by Chan et al reported approximately 75% preferred to use the IV route[7] but Spain et al noted that the first dose was usually given via the intramuscular route and subsequent doses were given intravenously[39]. The NICE guidelines stated a preference for the intramuscular route from a safety point of view[11].

IM route:

Advantages;

- Easier to rapidly administer
- No requirement of intravenous access

Disadvantages;

- Slower drug absorption and action of onset
- Larger initial doses required, no titration.
- Less predictable outcome with some drugs

For sedation of ABD most guidelines suggest intramuscular sedation [49, 63, 78, 85]. In the acutely agitated and psychotic patient, the intramuscular route is an absolute necessity in such emergency situations and is reserved for the agitated patient for whom parenteral treatment is the only feasible option[20]. The major advantage of the intramuscular (IM) route is in

involuntary treatment [56]. The reason for this is the easy access and the rapid administration. A recent retrospective study comparing two different time periods where predominantly IV use was compared to a period after the introduction of a randomised controlled trial using IM only, demonstrated that the overall duration of ABD was reduced when intramuscular administration of sedation was employed as first line management due to easier and quicker access[86]. Evidence for the use of droperidol is particularly compelling for situations in which IM administration is necessary[87]. In a randomised controlled trial by Thomas et al[70] comparing haloperidol to droperidol it is stated that although IM administration is generally slower than IV, droperidol is an exception as it is absorbed so rapidly that there is little difference between IM and IV and the effect is considered predictable.

Drugs used for sedation of ABD

There are different classes of drugs which are available to achieve sedation and many drugs within each class. The best drug to use in this situation remains unclear and the decision is usually based on anecdotal evidence[88, 89]. The medical management of ABD is a critical situation which is difficult and inherently stressful and there is little evidence and a lack of consensus on appropriate treatment in this emergency situation[4, 90]. The requirement for urgent pharmacological sedation for the management of agitated and violent behaviour is an important and surprisingly under researched area [21, 62]. It is speculated that the reason for this lack of literature is due to the complexity and heterogeneity of the presentations of ABD patients and their lack of capacity to consent to treatment. It is an area fraught with ethical and legal dilemmas, together with difficulties associated with the management of these patients in a health care setting which is often chaotic and stressful[4].

In Australia benzodiazepines (predominantly midazolam) and antipsychotics (haloperidol and olanzapine) are the most commonly used drugs for sedation of patients with ABD and many clinicians prefer combination therapy[7].
The two major groups of medications used as parenteral sedatives for ABD are benzodiazepines (midazolam, diazepam, and lorazepam) and antipsychotics (haloperidol, droperidol, and olanzapine). Other agents are employed when these fail.
Benzodiazepines refer to any of several similar lipophilic amines used as tranquillizers, sedatives, hypnotics or muscle relaxants[11].

2.2.1 Benzodiazepines

Benzodiazepine administration in oral, intramuscular and intravenous preparations are thought to be effective in treating agitation that is not related to psychosis and are often used as a supplement to typical antipsychotics[56]. Many clinicians are in agreement with this which is reflected in the widespread use of benzodiazepines in the management of ABD. Benzodiazepines are the first line treatment for delirium that is associated with seizures or withdrawal from alcohol or sedatives[45, 84, 91]. The desired sedative effects necessary to control ABD are thought to be due to the binding with receptors in the central nervous system; these receptors cause an increased inhibitory effect of g-aminobutyric acid (GABA).

Diazepam

Diazepam is a benzodiazepine with CNS depressant properties and a somewhat flatter dose-response slope than the sedative-hypnotic drugs. Some benzodiazepines such as diazepam, have erratic and slow absorption intramuscularly and are associated with prolonged sedation following repeated doses[11]. This restricts the role of parenteral diazepam in the treatment of ABD when venous access is not achievable. The slower off-set of action is also a consideration which restricts its use.

Midazolam

Midazolam is a water-soluble benzodiazepine, has anxiolytic, sedative with anti-convulsive characteristics. Midazolam is lipid-soluble and acts on the central nervous system quickly[92]. In Australia a very recent cross sectional mail survey of the Australasian College for Emergency Medicine(ACEM) indicated that midazolam is the most common monotherapy of choice in current clinical practise for sedation of the undifferentiated patient [80]. The use of midazolam for ABD is associated with over and under-sedation when use in benzodiazepine naïve and benzodiazepine tolerate patients respectively[28]. It is well documented that it commonly causes respiratory compromise[39].

Lorazepam

Lorazepam has a shorter elimination half-life than many other benzodiazepines, which limits the risk of excessive sedation due to the cumulative effects of the drug. For this reason it is often chosen as the first drug of choice in rapid tranquilisation[11]. However, Nobay et al compared lorazepam to midazolam in an RCT and demonstrated that the onset was more rapid with midazolam and overall they were equally effective [93]. Battaglia et al found it was effective in reducing agitated behaviour but was more effective when used in combination with haloperidol and required repeated doses. Similarly, Richards et al reported that it was less effective in the 202 cases of ABD compared to droperidol at 10 to 60 minutes and required 40 repeated doses compared to droperidol needing to be have 8 additional doses administered at 30 minutes[94]. Even though it is recommended in the Reference Guide for Mental Health for Emergency Departments[85], it is not commonly used as it is difficult to obtain in Australia as it requires a 5A pharmaceutical schedule by each hospital, has a shorter shelf life of only 12 months and is expensive in comparison with other drugs of this class ($45/ 5 vials).

2.2.2 Traditional Antipsychotics

There are two main categories of antipsychotics; typical and atypical. The distinction is not clearly defined but rests on the incidence of extrapyramidal side effects and the effectiveness against the negative symptoms of psychosis in atypicals. The major use of antipsychotic drugs is in the treatment of schizophrenia[95] but many of these agents possess sedative properties also and have been used therapeutically for his purpose as a result.

Their effectiveness in acute treatment in different populations remains poorly studied [96], however clinical experience suggests that antipsychotic agents generally have a good margin of safety [97] even at high doses,. Important pharmacological features of the

antipsychotic drugs include their extremely high therapeutic index (the ratio of a toxic dose to a dose that produces noticeable behavioural effects) and resulting lack of lethality [30].

Antipsychotics are not addictive, partly because they produce no euphoria. As of now, comparative effect and safety data confined to individual antipsychotics agents are difficult to assess from literature [98]. Both haloperidol and droperidol are the most commonly used parenteral typical antipsychotics. Chlorpromazine is often used orally for sedation in patients especially in the mental health setting.

Haloperidol

Haloperidol is a butyrophenone antipsychotic and a dopamine(D2)-receptor antagonist that is used in the treatment of schizophrenia and acutely in the treatment of acute psychotic states and delirium. Haloperidol possesses a strong activity against delusions and hallucinations, most likely due to an effective dopaminergic receptor blockage in the mesocortex and the limbic system of the brain[95]. It blocks the dopaminergic action in the nigrostriatal pathways, which is the probable reason for the high frequency of extrapyramidal-motor side effects[99]. A trial using 3 treatment arms of Lorazepam 2mg , haloperidol 5mg or both and the combination of the therapies doubled the dose of the combination treatment over the other arms. Battaglia et al reported extra pyramidal side effects between 6-20% given that the treatment could be repeated up to six times in the study period. In 2007 Huf et al compared Haloperidol alone verses Haloperidol plus promethazine in 311 patients. The combination arm was more likely to be asleep by 20 minutes but remained the same after additional doses used in the combined group added up to 50 mg of promethazine to the original dose. Haloperidol alone had 10 patients with dystonia[90]. Three years later Baldacara et al used 5 treatment arms. Three were single agents, olanzapine, ziprasidone and haloperidol to the other two arms was the combination of haloperidol with promethazine and haloperidol with midazolam. Midazolam plus haloperidol had the poorest outcome as it was considered more rapid but was associated with over-sedation and rebound aggression[100]. Since then haloperidol was imposed with a black box warning for QT prolongation and has been associated with an increase risk of death[101, 102]. Most recently the randomised control trial of Haloperidol verses droperidol in the psychiatric intensive care unit showed no significant statistical difference between groups in the time to sedation or frequency of adverse events[27].

Droperidol

Droperidol is related structurally and pharmacologically to haloperidol. It is a butryphenone antipsychotic. Butryphenones were initially studied in the late 50s in the Janssen laboratories in Belgium as a substitute for morphine[103]. It produces general quiescence and a reduced responsiveness to environmental stimuli in several animal species. In humans it produces marked tranquilisation and sedation. It was soon realised as a useful treatment of psychosis[104]. It exhibits blockade of the post-synaptic-D2 receptor, this results in its therapeutic benefits as an anti-emetic and antipsychotic. It has been demonstrated that it has selective effects on the alpha1, adrenergic, serotonin and histamine receptors[105]. It has been well reported for the treatment of migrane [106, 107], vertigo[108] and as adjuvant therapy with opioids not only for its anti-emetic properties but also to precipitate the analgesic qualities of

the pain relief medication such as morphine[109]. Indications included by Mims on-line are for "Management of severe agitation, hyperactivity or aggressiveness in psychiatric disorders[110]. Compared to haloperidol it is reported to have a more rapid onset of action, shorter duration of effect, and lower incidence of extrapyramidal symptoms[70, 111]. The benefit of using droperidol in the emergency department for treating ABD is its rapid offset[29]. Droperidol has an apparent elimination half-life of 2.2 hours after IM administration compared to 10 to 19 hours for IM haloperidol[112]. This is an important factor when emergency departments' length of stay is a key performance indicator measured in minutes in all public hospitals throughout the developed world. In a randomised controlled trial Richards et al found the total time in the emergency department was significantly less for droperidol, 5.9 hours, compared to 8.6 hours for lorazepam[94]. Droperidol was issued with a BBW concerning cardio-toxic effects[113] . Prior to this it was effective in controlling ABD to and enable diagnosis and treatment[96]. Droperidol has been used for decades with a sound safety record[114] and was commonly recommended by experts specifically for severe agitated behaviour and physical aggression[49]. Since the BBW it has effectively been removed as the cornerstone drug to treat ABD in the ED. This has sparked controversy in the literature regarding the validity of the evidence and if the warning was warranted[115, 116]. Recently, droperidol has been replaced by new generation antipsychotics (atypical) and older antipsychotics such as haloperidol due to lack of availability and fear of litigation.

2.2.3 Second generation antipsychotics

With the introduction of clozapine in 1989, second generation antipsychotics (atypicals) have continued to be developed. They differ from first generation antipsychotics in that they have additional receptor site activity beyond the central dopamine-2 receptors sites. They block receptors of several neurotransmitters in the brain including alpha-1, dopamine, histamine H-1, muscarinic, and serotonin type 2 (5-HT2) receptors. They provide less potent blockade at the D2 receptor site. This lowers the rates of extrapyramidal side effects[44, 117, 118]. Atypical antipsychotics include clozapine, olanzapine, quetiapine, risperidone and ziprasidone. As with most antipsychotics they are predominantly used to treat chronic mental illness. Yet Olanzapine has been marketed as having a role in the treatment of ABD. The utility of atypical antipsychotics in the emergency setting has been relatively unexplored because of low titration schedules or dose limiting adverse effects for some members of the class (clozapine, quetiapine, ziprasidone) which have made these agents impractical[56].

Olanzapine

The only atypical used parenterally for ABD is olanzapine with limited proven effectiveness in the emergency department setting. The recent multi-centre trial by an Australian group reported inconclusive results in a trial in the ED of intravenous droperidol or Olanzapine both with midazolam [119]. They concluded Droperidol was equally effective as Olanzapine yet droperidol needed less additional parenteral sedating drugs to reach initial adequate sedation 12.5% compared to 18.4%[119]. Olanzapine is not FDA approved for these indications. It was approved by the FDA in 1996 to treat schizophrenia and acute manic episodes associated with bipolar disorder and rapid control of agitation. The therapeutic guidelines section on behavioural emergencies in acute psychiatric setting caution intramuscular olanzapine should

not be used concurrently with benzodiazepines and other central nervous system depressants owing to the risk of cardiorespiratory depression, hypotension and bradycardia[47]. Olanzapine has been included on clinical practise guidelines for treatment of ABD. The role of these agents for ABD has not been tested in the clinical setting fully as studies are confined to the psychiatric setting only[60, 100, 120, 121] or the trials are industry sponsored studies[46, 120]. There are safety concerns regarding the combination of olanzapine and benzodiazepines and this combination is not recommended by the manufacturer due to the risk of profound hypotension. A retrospective chart review has confirmed that this combination has additional risk if combined with alcohol[46]. Further there are case reports of 29 patients with adverse effects of elderly patients treated with olanzapine for ABD which conclude that concurrent olanzapine and benzodiazepines are not recommended especially in the elderly[122]. Considering the patient profile who regularly attend the emergency department these restriction are prohibitive of the role of second generation antipsychotics for undifferentiated ABD. Additionally all second generation antipsychotics have been shown to prolong the QT interval at steady state plasma concentration at their maximum recommended dosage[123] which is the primary reason for droperidol being not used for this purpose.

2.2.4 Comparisons of drugs

A number of antipsychotic medications have been used for the treatment of ABD, but they are often not very sedating, such as haloperidol. There is agreement with this in an extensive review of literature between the years of 1960-2002 by Shale et al, the authors concluded that in clinical practice droperidol is extremely effective and safe method of treating severely agitated or violent patients [124]. In the Cochrane Review, Cure and Carpenter state that droperidol is more effective than haloperidol "albeit on limited evidence" [62]. Richards et al agrees that sedation is somewhat greater with droperidol than with haloperidol, making it ideal for use in the ED [36]. Dopamine receptor blockade is less clearly related to the tranquilising effect and some antipsychotics are more sedating than others [97]. The sedative qualities of others such as chlorpromazine are associated with significant adverse effects such as hypotension. Olanzapine has been suggested as an option, however there are no studies of its use in the emergency department for sedation of patients with ABD[58, 120, 125]. Olanzapine is associated with delirium itself in overdose[125] so may not be the ideal option for ABD in patients.

The butyrophenones (haloperidol and droperidol) are leaders in the pharmacological arena for chemical restraint [30, 36, 70, 82, 93, 94, 126, 127]. In one survey in the West of Scotland haloperidol and droperidol were the main stay for rapid tranquilisation based on findings from 180 respondents[128]. Droperidol lacks the pronounced cardiovascular effects found with some of the phenothiazine neuroleptics[129]. The onset of action is 3 to 10 minutes given via the intramuscular or intravenous route. When administered parenterally the blood concentrations increase rapidly because it avoids first-pass metabolism in the liver, which occurs with oral administration[97]. If the patient is very active or involved in violent activity, as is the case of acute behavioural disturbance, the rate of absorption from an intramuscular injection will be faster than in a quiet patient as the blood flow to the muscles is much increased. In rats

droperidol has a 10 fold higher median lethal dose than haloperidol [87]. During the period from 1973 up until the black box warning in 2001 there were only 5 comparative drug studies on the use of droperidol for ABD. Two were placebo verses droperidol randomised controlled trials[71, 130] whereby the results, not surprisingly, were highly significant in the effectiveness of droperidol. In the comparative drug trials all the results were in favour of droperidol as opposed to its comparator. The comparator in two of the three studies was haloperidol [70, 126], and lorazepam as comparator in the third study of the five [94]. In the largest prospective randomised study, Richards et al found total time in the emergency department shorter and less need for additional sedation with droperidol. Again an increased need for additional injections were need to achieve sedation by using a sedation scale in the Resnick et al study in 1984, whilst Thomas et al found droperidol to have a faster onset of action than haloperidol. Just prior to the release of the black box warning , a pre-hospital pilot study of 53 combative patients en route to the ED concluded that droperidol was both effective and rapid in this setting [69]. This limited number of studies calls for further randomised controlled trials and safety studies to reinforce these convincing findings[131]. Droperidol is favourable due to its lack of respiratory compromise. In the study by Knott comparing Droperidol to Midazolam there was a similar frequency of adverse events except the respiratory distress caused by Midazolam resulted in the need for airway intervention in 3 patients one of which needed to be ventilated[132].

4.0 Adverse drug effects

There are a multitude of adverse effects associated with drugs used to treat ABD. These include cardiac effects, respiratory depression, airway obstruction, hypotension, extrapyramidal side effects, seizures and rarely neuroleptic malignant syndrome[133]. The NICE guidelines note that parenteral treatment of ABD may lead to deep sedation/anaesthesia as any sedation has unpredictable effects. It is generally accepted that poly-pharmacy should be avoided and medication doses ideally should be as low as possible to decrease the associated risk of adverse effects[51, 134].However, the necessity to administer high and above the recommended dosages for ABD is recognized and accepted practice[51, 134] and commonly at higher than normal recommended doses[135]. Potential life-threatening complications of pharmacological therapy should be anticipated, which may include respiratory depression, hypotension and extrapyramidal side-effects. This is of particular importance in the mental health setting where there is less access to resuscitation expertise [47]. Larger doses increases the risk associated with any agent given. Studies with investigation of larger doses have a corresponding adverse event rate larger than those with more conservative doses. The Spain et al trial on the Gold Coast with midazolam given in 10 mg increments at 10 minute intervals resulted in 24% of the patients failing one or more of the safety criteria[39]. In the psychiatric setting many studies focus on sedation of ABD on the level of patient aggression[136], and vital signs are frequently under-reported and true complication rates are difficult to assess[137]. Most studies done in the ED include adverse effects reported predominately from vital signs as the primary and secondary outcome[70, 93, 94, 119, 132, 138]. This reflects the emphasis the ED has on recording measurable clinical signs which is routine practice. When repeated attempts additional doses and agents have failed the ABD fall into

the category of difficult to sedate. Alternative agents are used as a last resort to manage these patients. Dexmedetomidine is a relatively selective alpha 2-receptor agonist with sedative properties. It is noted for its lack of suppression of the respiratory drive[139-141]. Not having previously been used for rapid sedation in the emergency department for ABD it was chosen for the purpose of investigating if it could be used in difficult to sedate patients on the grounds of its effectiveness in the intensive care setting to sedate with less respiratory depression. A pilot study was conducted to investigate if it had a role in the emergency department setting. Of the thirteen patients in this study only 4 remained sedated for a period of one hour and six of the thirteen had a significant drop in blood pressure which required the infusion to be titrated down. This adverse event rate suspended the study and dexmedetomidine was not recommended for treatment of ABD within the setting of the emergency department[142].

4.1 Adverse effects of Benzodiazipines

The disadvantages of managing ABD with benzodiazepines is the association between respiratory depression and excessive sedation especially when coupled with alcohol. Less common are paradoxical excitement, hypotension, confusion, disinhibition, headaches, ataxia, and anterograde amnesia[29, 49]. In the elderly, benzodiazepines places patients at a higher risk of adverse events including cognitive impairment, delirium and falls and a clinical guideline warning was released in March 2014 cautioning the prescription of benzodiazepines to patients over 65 years of age[143]

All benzodiazepines cause respiratory depression and is the commonest most important adverse effect of this class of drug[99], especially when given in high doses or when used in combination with other sedative agents, including alcohol[144]. Within 6 months of the approval of midazolam for use in the United States in 1986 this drug was associated with 13 fatalities related to respiratory depression and cardiac arrest, particularly in the elderly. Despite lowering the recommended dose, by 1990 the number of associated deaths had risen to eighty one[145]. Concerns of the use of midazolam in the elderly have led to recommendations for a reduction of the IM dose by up to as much as 50% due to adverse effects from excessive sedation [146, 147]. A poor safety record was reported in a more recent study in Queensland in which eight of 62 patients had a GCS< 8 for more the 30 minutes with airway adjunctive supports being required in 4 of 62 patients due to over-sedation[39]

Other studies reported the risk of respiratory depression such as Martel et al where oxygen was required in 10 of the 48 patients with midazolam 5 mg IM[2]. In the prospective randomised trial of midazolam verses droperidol by Knott et al reported 4 of the 74 patients receiving midazolam experienced airway problems and hypoxia[132]. This highlights the need for judicious use in patients intoxicated with alcohol or benzodiazepines[28, 56, 96]. Yildiz et al cautioned the use of benzodiazepines in patients with respiratory difficulties describing the treatment as potentially dangerous[20]. The respiratory adverse effects of midazolam are well documented [55, 117, 145] and in the review article of the therapeutic uses and toxicity of midazolam, particular concern was expressed by Nordt et al for the safety aspect in the treatment of ABD[145]. Contrary to this however, the Expert consensus guidelines [117] in May

2001 recommended benzodiazepines in the "Medication by Etiology" section as the preferred drug to be administered in the event of Alcohol Substance Intoxication which is a diagnosis known to cause respiratory depression. In most guidelines recommending the use of midazolam, Flumazenil is required to be available in the event of respiratory depression. This is contrary to current clinical practise which encourages airway support as the risk of inducing seizure activity from reversing the benzodiazepine using flumazenil remains a potential risk[148].

Benzodiazepines can cause hypotension especially in high doses[49, 99]. Drug induced hypotension usually manifests in the form of postural hypotension, symptoms are usually transient and include headache, blurred vision, dizziness and syncope. There is a risk between low blood pressure and cardiovascular implications, however no lower threshold of normality has been identified[149].

Paradoxical excitement can be in the form of excessive anxiety and tremulousness, hyper-excitability, confusion, and hallucinations. These have all been reported in association with the use of benzodiazepines. Delirium is common, particularly in the elderly who may have impaired drug clearance and the cause of drug induced delirium possibly from benzodiazepines must always be considered[99]. Benzodiazepines can cause disinhibition and this seems to be more common in short acting benzodiazepines[49]. Disinhibition can exacerbate the severity of the ABD and therefore at times would be considered contra-indicated.

The effect of intramuscular midazolam is unpredictable and can lead to over- or under-sedation and is associated with complications due to benzodiazepine tolerance in this patient group[28]. A major disadvantage of using benzodiazepines for sedation is tolerance which develops with all benzodiazepines[150], this is considered by many clinicians as the main drawback [151]. If benzodiazepines are used regularly, which is often the case in this patient population, the patient will develop tolerance to the effect. Benzodiazepines act on the gaba receptors and have the capability of blocking the transmission of impulses within a 6 hour dosing period [152]. The effect of the drug gradually diminishes when it is given continuously or repeatedly administered, this is pharmacologically defined as desensitisation. This phenomenon can develop in the course of a few minutes [95]. Spain et al clearly demonstrated poor effectiveness in their randomised controlled study reporting seven of 62 patients (11%) were not sedated, despite four 10mg doses of parenteral midazolam[39].

4.2 Adverse effects of Antipsychotics

Drug treatment of ABD requires careful consideration of the balance between the effective management of symptoms and potential side effects [96]. Extrapyramidal side effects (EPS) vary greatly in symptoms and severity, from mild tics to life- threatening laryngeal dystonia. Extrapyramidal side effects are more commonly associated with conventional antipsychotics. They are a cluster of symptoms and signs that include dystonia, involuntary movements, tremor and rigidity. EPS are the direct consequence of block of the nigrostriatal dopamine receptors located in the basal ganglia region of the brain. [95] These symptoms can frighten

patients and lead to reduced compliance with regular antipsychotic treatment, and may aggravate agitation or uncontrolled behaviour[153]. The most common EPS are dystonic reactions which is not dose related [154] and include involuntary turning or twisting movements of muscles usually of the back neck and oral area. The treatment for dystonia is anticholinergics or benzodiazepines.

A related side effect that can be frequently misdiagnosed is akathisia (Greek word meaning "inability to sit still"). It is actually a symptom and the patients usually describe the feeling. Although grouped with EPS the pathophysiology is poorly understood and there are not clear treatment guidelines. Akathisia has the potential to contribute to the ABD and the increased restlessness can be mistaken for exacerbation of the ABD instead of a side effect of the antipsychotic given to treat the ABD.

The occurrence of EPS including akathisia, in the first 24 hours after rapid tranquilisation appears to be low and rarely do patients require treatment [30]. Haloperidol is known to cause more side effects as noted by the mail out questionnaire to ED physicians in Scotland[128]. Thomas et al [70] in 1992 conducted a randomized control trial involving sixty eight violent or agitated patients and reported droperidol resulted in more rapid control of patients than haloperidol without any increase in undesirable adverse effects. Similarly in other studies of sedation of ABD droperidol rarely causes akathisia or dystonic reactions, one patient in 50 (2%) was reported by Martel which was akathisia [2], three patients in 76 (4%) developing dystonic reactions in the study by Knott et al[132], one dystonic reaction in 102 (1%) having dystonia in the study by Richards et al [94], 26 in 2,468 (1%) requiring rescue medication for dystonia or akathisia in the series reported by Shale et al [124] and more recently 2 patients in 73 with low dose droperidol to treat headaches in the ED was reported by Faine et al[155]. Exceptions to the findings of only 1-4% of EPS are the studies of Miller et al and Weaver et al who had dystonia and akathisia rates of 7.3 and 10.5%[156, 157] of droperidol for the treatment of headaches. Another exception is the case series report by Richman et al who had akathisia occurrence at 13.3% but this was a very small sample size of only 29 patients[158].

In the mental health care setting it is common practise to administer benzetropine prophylactically to prevent the occurrence of EPS. This practise has been poorly researched and issue of prophylactic treatment during rapid tranquilization is unresolved and is given due to clinicians preference.

One area of controversy and significant concern, is the potential for antipsychotic agents to produce QT prolongation. This is addressed in the next section.

4.2.1 Cardiac effects of antipsychotics

The adverse effect which has made a considerable impact on the use of typical antipsychotics in general and most specifically droperidol, is the potential to cause drug induced QT prolongation which has been known to precede the arrhythmia Torsades des Pointes (TdP). There is a dose relationship between high doses of droperidol and haloperidol and QT prolongation have been reported [159]. Ten of the eleven reported cases which prompted the FDA warning for droperidol occurred in doses ranging from 2.5mg to 600mg [116] and these

cases occurred in patients with significant co-morbidities and routine poly-pharmacy which is known to increase the risk of arrhythmias [160].

The QT interval is the period in the cardiac cycle from start of depolarisation of the ventricle to the completion of ventricular repolarisation. A number of cardiac and non- cardiac medications such as antipsychotics prolong this interval. The mechanism whereby this occurs is the delayed repolarisation secondary to effects on potassium efflux during the repolarisation stage of the action potential. Drugs can impair the rapidly activating delayed rectifier potassium current (I_{KR}) thus theoretically inducing prolongation of the QT interval[159]. TdP is usually self-limiting and usually occurs with bradycardia following an early after depolarisation beat generating a re-entrant circuit[161]. TdP is defined as a polymorphic ventricular tachycardia characterized by a 'twisting of the points' around the isoelectric line on the electrocardiogram (ECG), and is preceded by a long QT interval[162]. Whilst a run of TdP by itself may not have ultimately adverse consequences for a patient, this arrhythmia does have the potential to degenerate into ventricular fibrillation and thus cause sudden cardiac death.

Although QT prolongation is associated with increased risk of TdP, the precise relationship is not well defined [163]. It is referred to as a marker to identify potential risk. Shah et al argued that a QT corrected for rate (QTc) is a poor indicator of TdP as this arrhythmia can occur at various QT lengths. This group identified a combination of factors which can cause TdP; termed TRIaD. TRIaD is the acronym for Triangulation of action potential, Reverse use dependency, Instability of action potential and Dispersion as predictors of pro-rhythmic properties of drugs[164]. As has happened in the past many case reports describe patients undergoing surgery under a general anaesthetic[165-168] and reports are complicated by inaccurate measurement techniques and flawed rate correction formulae or lack of them used. To identify the agent responsible for QT prolongation under a general anaesthetic is difficult due to the contribution of the many agents used. There are many studies examining the effects of different anaesthetic agent on the QT interval and all volatile anaesthetics prolong the QT interval to some extent[169]. Drug induced cardiac conduction changes and arrhythmias are exacerbated by multiple factors, including electrolyte abnormalities, structural heart disease, genetic disposition, and drug-drug interactions[170] Other causes of variability are the naturally occurring diurnal changes of the QT related to heart rate (HR) effect on the QT interval which occur over the 24 hr period [171, 172], and the concept of heart rate correction ignores the dynamicity of QT/R wave to R wave (RR)relationship. Clarification is needed regarding the best way to measure the QT interval and the degree of prolongation that is considered significant.

4.2.2 Causes of QT prolongation

A summary of the causes of QT prolongation is as follows:

- Congenital /genetic [161, 173]
- Bradycardia (sleep)[161]
- Age [102, 174, 175]
- Gender -Testosterone is protective because during puberty the QT shortens in males[174]

- Cardiac Co-morbidities - Ischemia [176]
- Prescription Drugs [173]
- Illicit drugs Cocaine, amphetamines, heroin[177]
- Sympathetic drive / sleep[178]
- Diurnal variation[179]
- Anorexia nervosa[180]
- Electrolyte imbalance[102] (K, Ca, Mg)
- Alcoholism[102, 181-183]
- Bradycardia [184 161, 185, 186]
- QT/RR Hysteresis[161, 172, 187-189]

4.2.3 Measurement of the QT interval

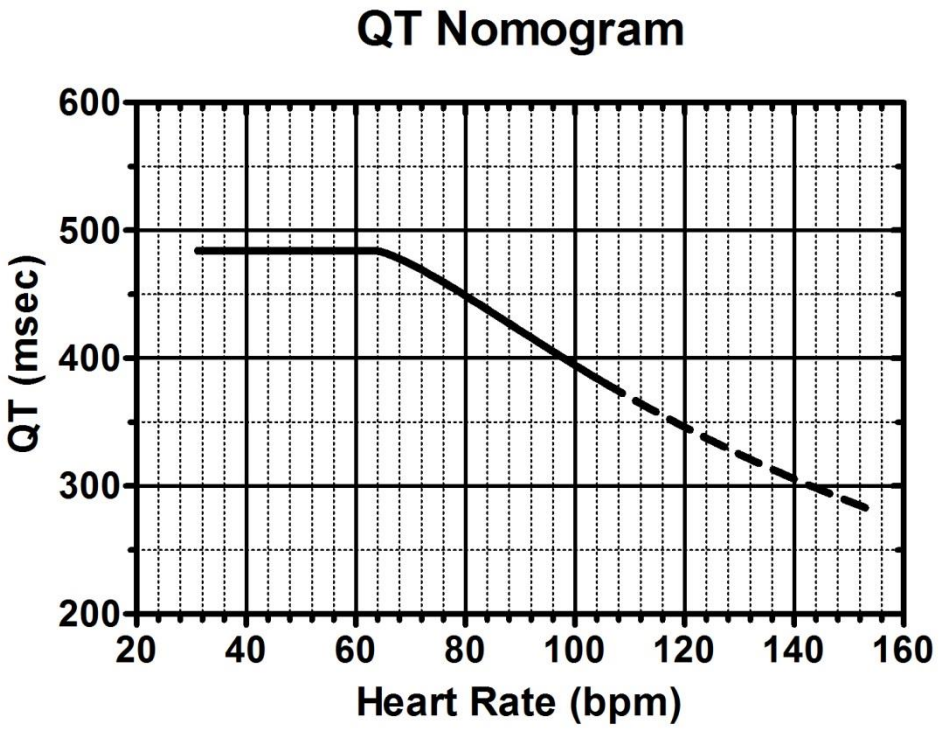
No standardisation exists to accurately measure the QT interval. On the electrocardiograph the wave form represents the flow of ions in and out of the cardiac cells. The rapid inflow of positively charged ions of sodium and calcium results in depolarisation and when the outflow of potassium ions exceeds this myocardium repolarisation occurs[190]. The accurate measurement of the QT interval and its correction or adjustment for cycle length(i.e. heart rate), age and sex have been the topics of significant contention of the past 70 years [191]. Accurate measurement of the QT remains problematic and despite good although modern algorithms for measurement of the QT, accurate measurement still requires manual review of the QT using on-screen magnification and callipers [192] The use of automated measurement of the QT interval using standard ECGs is not accurate or reliable enough to be used [171, 193]. [171, 193]. Factors such as flattened and abnormal T waves, noise in the signal and lack of T wave and U wave distinction may lead to invalid readings and it is considered safer to use manual measurements[171]. Yet recently a paper has claimed with the advancement of technology the accuracy of automated measurement has improved except in cases of abnormal ECGS[194] Notably the newer algorithms measure from the beginning of the earliest Q wave onset to end of the slowest T wave off-set. Invariably the readings are usually longer and it is recommended by the International Society for Computerized Electrocardiography that a visual review and careful consideration should be applied to all prolonged QT measurement and abnormal ECGs tracings using the new algorithms[194]. The manual measurement also has no universally accepted method of measurement. As far back as 1952 the recommendations for measurement were controversial, one such example was to measure the QT interval in all leads and the lead with the longest interval should be used[195]. This was criticised as erroneous if the difference in leads was more than 40ms. The variation in the recommendations of measurement vary broadly such as methods to measure in a single lead(most commonly Lead II), or in the lead with the most prominent T wave[196], however in cases where dispersion exists across the tracing the longest lead length has been recommended to be used[191]. Other methods include a limb lead that best shows the end of the T wave[197], however Malik states measurement in any one lead is imprecise[198] and advocates that even measuring one cardiac beat in any lead is insufficient. Rather 3-5 beats in each lead are measured and the results of these are to be averaged. The quasi-orthogonal system of the taking the earliest

q wave onset to the end of the longest T wave offset in I, aVF and V2 has been criticised as it does not take into account the variability of the cardiac axis[171]. A practical alternative to measuring 3-5 beats in all 12 leads has compromised Malik's method by measuring 6 leads which appears to be accurate on a standard ECG as long as a median QT is taken [193].
U-wave abnormalities remain problematic. Consideration is needed of whether to include the u wave in the measurement when there is not a return to baseline. Also when the U- wave and T-wave are superimposed and cannot be separated causes difficulties. Some suggest only reading the QT interval in those leads not showing u waves or that the downslope of the T-wave be extended by drawing a tangent to the steepest proportion of the downslope until it crosses the baseline[199, 200].This method was originally designed back in 1952 and is acknowledged by Malik but only in the instance when the T-wave and U-wave cannot be separated[195].

4.2.4 QT Correction formulae

A major challenge in electrocardiology is not only the accurate measurement of the QT interval but also its correction for rate[199]. There have been significant problems with the use of HR correction formulas that produce a corrected QT, including Bazett's formula, the most commonly used correction method[163]. Another common correction formula is that of Fridericia's. These correction formulas are represented mathematically as $QTc=QT/RR^{\alpha}$ where alpha is the correction of the QT for the heart rate (HR). Alpha has been found to stay relatively constant for each person but varies greatly between individuals[171], which means that an individual alpha for each patient is required. The usual approach is to use alpha = 0.5 (Bazett's) or alpha = 0.33 (Fridericia's) for the whole population which leads to inaccuracies. These HR correction formulae result in significant over-estimation of the QTc in tachycardia and an under-estimation in bradycardia [163, 171]. Alternative methods not requiring a constant numerical alpha are Hodges formula ($QTc=QT+1.75(HR-60)$[201] as recommended by the American Heart Association guidelines [199], and Framinghams formula $QTc= QT+154(1-60/HR)$[202]. The concept of heart rate correction ignores factors such as the effect of QT hysteresis[203] . Other causes of variability are the naturally occurring diurnal changes of the repolarisation related to heart rate effect on the QT interval which occur over the 24 hr period[171]. The significance of overestimation of QTc in tachycardia and an underestimation in bradycardia[204] accounts for the reason the QT nomogram out-performs the bazetts formula when applied to cases of TdP. This alternative method to assess the risk of TdP by using the QT nomogram[163](diagram 1) is it provides a different approach to the assessment of pro-arrhythmic risk in QT prolongation. It does not require the use of correction formulae or numerous previous ECGs required for individual HR correction[163]. For this reason it has proved to be clinically practical. The correction for heart rate is by visual inspection. The greater the orthogonal distance of the plotted QT interval from the line on the nomogram indicates a greater risk of TdP[184]. Values of the QT/HR pairs plotted within the area below the "at risk" line the QT is considered to be normal for that heart rate[193].

Diagram 1: QT Nomogram



5.0 Black box warning (BBW) of droperidol

Droperidol received a BBW in 2001 and that effectively lead to its demise as a therapeutic agent. The evidence to support this action taken by the FDA was based on a publication in The Lancet by Reilly et al[205]. They reviewed ECGs obtained from 101 healthy reference individuals and 495 psychiatric patients to assess QT interval abnormalities[205]. The group did not account for the independent variables such as age and sex in the statistical analysis. They confirmed that there was a dose dependent prolongation of the QT interval. Reilly et al calculated the QT intervals as the mean and not the median, of the 12 leads which were corrected by Bazetts formula which skewed the results unfavourably for droperidol.

A black box warning is the strongest form of warning issued by the FDA about a drug and, the step taken just short of removing the drug from the market. It is an alert of how harmful the drug can be if given to patients who are at risk of developing possible adverse effects. The Medicines Control Agencies UK initially raised a safety concern regarding the chronic use of high dose droperidol in psychiatric patients.[104] Jansen Cilag Ltd , the founding firm of droperidol soon after withdrew production of all forms not just the oral preparation. In December 2001 a black box warning was added to the package insert prescribing information on droperidol which called attention to the potential cardiac toxic effects. The revision to the prescribing information on droperidol supplied with the drug included information on the risk of QT prolongation and reports of death, and recommended that it be used secondary to other options and used with extreme caution. The warning called for mandatory electrocardiograms(ECG) prior to use[113]. The founding manufacturer of droperidol (Jansen-Cilag) voluntarily withdrew it from the market worldwide in, after reports of QT prolongation, serious arrhythmias, or sudden death in association with its use. The Canadian Health Protection Branch followed with a warning soon after[206]. In the United States,

droperidol remained available from other manufacturers although its use was restricted to the management of nausea and vomiting after surgical or diagnostic procedures . Prior to the FDA imposing a black box warning on droperidol, the pharmaceutical company Janssen-Cilag reported fifteen low dose adverse events on a single day in July 2001 . These reports spanned a period of approximately seven and a half years and they included 8 deaths attributed to droperidol. Janssen – Cilag only reported these cases three months after it stopped selling droperidol as an antipsychotic in Europe. Janssen-Cilag markets the leading antipsychotic, risperidone (risperidol) in the United States [207], and they clearly stated that the withdrawal of the injectable form of droperidol was for commercial reasons and not for reasons of safety [128]. In January 2001 Janssen-Cilag wrote to healthcare professionals to inform them that the droleptan (droperidol) product range was to be withdrawn because of a risk benefit analysis that had highlighted the potential effect on droperidol on the cardiac QTc interval. The oral presentation was to be withdrawn to prevent its use in "chronic conditions". The reason for withdrawal of the injectable form was "commercial viability". Akorn in the United States, the manufacturers of Inapsine (droperidol), wrote a similar letter to the health professionals on December of the same year and added " important changes" to the Inapsine labelling to include the black box warning and changes in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections. The dose was restricted to low doses for use as an antiemetic.

Since the FDA warning, and the subsequent withdrawal and lack of availability, controversy has increased, and there has been extensive debate in the anaesthesiology literature as these actions have essentially removed one of the most effective and cost effective anti-emetics from clinical use [208, 209]. Many believe that this warning was unjustified given the efficacy of droperidol as an antiemetic, the lack of published evidence of droperidol induced arrhythmias during decades of use, and the absence of overt toxicity at low doses. Nuttall describes it as "excessive and unnecessary" [210] after retrospective study evaluating over 16,000 cases of droperidol use. There is a considerable body of evidence disputing the validity of the reports and the poor quality of evidence supporting the black box warning [115, 207, 209, 211-216], and most of what is known about drug induced QT interval prolongation derives from spontaneous reporting mechanisms[217] and unfortunately these anecdotal reports are not peer reviewed [218]. In a recent multi-centre blinded RCT of olanzapine verses droperidol when administered with midazolam there was no difference in the QTc between groups from 211 ECGs obtained. The median QTc of the control group was 444ms, droperidol 441ms, and olanzapine 448ms. The only QT prolongation detected was in the olanzapine and control groups[119].

5.1 Controversy of the safety concerns of droperidol

Prior to a black box warning issued for droperidol in 2001 by the United States Federal Drug Administration(FDA) droperidol was the most commonly used and recommended drug to treat ABD[49, 128]and was considered standard clinical practice[2, 84, 124]. Although the usefulness of droperidol in the treatment of ABD has been established over decades [2, 70, 114, 215, 219, 220], its safety has been questioned in regard to its cardiac toxic effects. However this is a

controversial assertion, as many clinicians and researchers doubt the validity of this claim [115, 208, 209, 211, 212, 215, 216, 221, 222]. The black box warning resulted in a rapid decline in the use of droperidol, despite decades of use for sedating patients with ABD. The degree of interest in this controversy has prompted many reports[115], studies[28, 205, 210, 218, 220], surveys[7, 128], publications[196, 209, 211, 215, 216, 223, 224], letters /- editorials[208, 212, 218, 225-229] and reviews[62, 124, 221, 222, 230].Despite this body of evidence droperidol has not been re-introduced into institutions for the role of managing ABD and consequently safety has been compromised for both the patients and staff. There is considerable controversy over why the black box warning was issued on droperidol. Many of these reports of adverse events were involving unacceptable high doses with many confounding drugs and co- morbidities. Duplicates and outdated data were included in the report. Kao et al conducted an extensive review of the literature concerning case reports of droperidol and prolonged QTc [115]. Seven case reports were analysed. Four of the seven patients cases cited developed TdP. Two of the seven did not but have prolonged QTc. In one of the cases neither were reported. It is apparent that each case reported had factors that are known to contribute to a prolonged QTc interval these included electrolyte disturbance prior known QT prolongation, cardiac disease and concomitant pharmacological medication known to produce long QT. Horowitz et al analysed 271 voluntary reports to the FDA 71 of the 271 voluntary reports that included 55 deaths were reported on the same day July 9th 2001 [215]. As a governmental watch dog for drug safety the Federal Drug Administration (FDA) evaluates the profile of drugs using a variety of data sources and a black box warning is the most serious indictment on a drug. However the validity of some of the reports is questionable including the deaths attributed to droperidol that were used as evidence of the risk association. One death was in a patient taking unspecified illicit drugs, another was a death 48 hours after the dose of just 5mg, another was in a patient with significant heart disease. Therefore there is little wonder why there has been continued interest in uncovering the validity of the black box warning.

Halloran and Barash examined the droperidol black box warning saga for three reasons. First, to understand the weaknesses in this aspect of drug review and safety process of the FDA. Second to restore droperidol use to clinical practice and third to involve physicians to be proactive in the drug safety reporting process [221]. The main drawback of the data mining of the FDA Adverse Event Reporting System is the bias affecting spontaneous reports which include the lack of details necessary to assess causal association, a generalized under-reporting and most importantly in the droperidol case, an over-reporting for drugs involved in safety alerts (notoriety bias), reporting rate by the duration of time on the market, termed - the Weber effect. Lastly the quality of data which includes missing information and extreme duplication and multiple records [214, 231]. Spontaneous post marketing reporting does not define the population from which the reports arise, leading to poor estimation of the incidence of adverse drug reports especially in long term use[232]. These flaws in the systematic reporting are particularly applicable to droperidol as it has been on the market for over 30 years and subject to most of this bias.

The black box warning consists of a warning that issued a contra indication of the use of droperidol in patients with known or suspected QT prolongation, and imposed the recording

of a 12 lead ECG before administration in all patients to determine whether a prolonged QT interval was present, and recommended that ECG monitoring be continued for a period of 2-3 hours after treatment to monitor for arrhythmias.
The statement of imposing a mandatory recording of a 12 lead ECG before administration made it very difficult to give to patients with ABD. Therefore for the indication of ABD treatment it has been has been effectively eliminated. Also, anaesthesiology at many medical centres across the US and abroad no longer use droperidol[218], stemming from fear of litigation and medico –legal concerns,[210, 227] despite a long and successful track record.
To help put the risk of mortality and morbidity associated with the administration of droperidol in perspective, Thompson has attempted to look at unexplained deaths in psychiatric patients. Unexplained rate of deaths in the admitted psychiatric patient in Australia account for 27 deaths per 100,000 patients as opposed to deaths by suicides are at a rate of 100 deaths per 100,000. However, the unexplained death rate in the general population is not known.[233] Thompson extrapolates on these figures to suggest many deaths assigned to the cause of antipsychotic association may well be undiagnosed sudden death from a multitude of other causes [97]. A recent review by the FDA found that at the time of marketing of droperidol in 1963 to October 2003 – a time period of approximately 40 years- there were 89 cardiac dysrhythmia- related events associated with droperidol administration. QT interval and TdP were responsible for 22 of these cases, 5 of them were fatal [234]. It should be noted that more than 25 million units of droperidol were sold in the year 2000 [115] giving some idea of the extreme rarity of TdP in relation to the amount of droperidol used.

To date the use of droperidol for ABD has been driven by experience rather than from evidence from well conducted and randomised controlled trials [62, 117]. It is now increasingly difficult to get sound evidence since the black box warning was issued in 2001. Concerns stem from the worlds reserves and availability of droperidol diminishing. It is no longer a treatment option in many countries of the world. Nuttall et al recorded a dramatic decrease between from approximately 12% between 1998 and 2001 to 0 % between 2002 and 2005 [210]. Further studies which are necessary will not be conducted due to these restraints.
Studies directly related to droperidol, and QT interval prolongation include eight prospective studies. Six of the studies were conducted after the black box warning on droperidol. All except Charbit in 2008, who used 16 healthy volunteers[213], used surgical patients as the patient population in their studies. Sneyd, in an editorial in 2009 described the effect of anesthetic agents and analgesia such as fentanyl as dynamic influences which complicates the QTc changes and is invariably associated with ubiquitous changes [229].These studies all include doses of droperidol prescribed for nausea and vomiting in the pre and post-operative setting [218, 235-237], which makes the relevance of the studies of limited value to the emergency treatment for the treatment of ABD where the doses required are four-fold to achieve rapid sedation. The few exceptions are the randomised controlled trial of droperidol or midazolam (DORM study[28]) and the droperidol verses olanzapine together with midazolam study [119]conducted in the emergency department for sedation of ABD. The trials included large doses of intramuscular droperidol and /or olanzapine , and included obtaining ECGs after sedation. There was no significant difference in abnormal QT intervals across all arms of the two studies. Isbister et

al concluded, in this setting, the therapeutic use of droperidol for sedation appears to be relatively safe, although larger studies using continuous 12-lead holter monitoring will be important[28]. Locally the preparation of droperidol concentrated in the 10mg in 2 ml formulation has led to a safer and more convenient administration. The preparation of 2mls, avoids the need to give two injections which reduces distress to the patient and has a reduced risk of needle stick injuries. The new formulation labelled as DORM™ is being used in large quantities by hospitals with access to the Therapeutic Goods Administrations(TGA) requirements for 5A scheduling restrictions .

Droperidol has subsequently been returned to the UK market in 2008 from another manufacturer, and its use remains restricted to the treatment of nausea and vomiting. It is only actively marketed in Brazil, the Czech republic, Scandinavia, France, Greece, Hungary, India, Ireland, New Zealand, Portugal and Spain for the control of agitated patients in acute psychosis and mania. The rationale for the restrictions remain unconvincing are engaged with no clear evidence base[4]. Inevitably, there are practical problems in studying this complex, ethically fraught area of clinical practise [4]. We are left with studying surrogate end points such as the phenomena of QTc prolongation as an indirect attempt at establishing the "safety" of droperidol. The current position adopted by the FDA leaves clinical scientists and practising physicians with a near impossible task –proving a negative [208]- and as Eger stated you can't disprove the existence of dragons [238].

6.0 Conclusion:

The literature review supports the need to address the concerns regarding the management of ABD and the need to fill in the gaps relating to monitoring and assessment. The decisions necessary to achieve successful sedation include choice of drug, dose, route and measures of effectiveness, monitoring and cardiac effects. These issues have been addressed in this thesis which is supported with peer reviewed publications. The need for further investigation is crucial to extend these findings into the wider use and importantly into the pre-hospital setting. Studies have shown that aggression is a serious problem in pre hospital emergency services[239]. In the pre-hospital environment dangers are magnified due to the remote setting, necessity for the patient extrication and transfer, and the limited number of staff available to deal with ABD[240]. In the pre-hospital setting paramedics and ambulance officers constantly encounter people with alcohol intoxication [241, 242]. The risk of harm is high as it is not a controlled environment and sedation can have unpredictable outcomes. Currently midazolam is the only drug permitted to be administered by Level 4 paramedics in the NSW Ambulance service for patient management[243]. Deep sedation is problematic as it requires monitoring and additional manpower to manage possible complications. Droperidol is a safer alternative which is equally effective in controlling the ABD in this setting.

There is a call to re-evaluate the pharmacological management of ABD and this only possible by providing data from well-designed trials and studies. The publications which contribute to this thesis have originated from an unmet clinical need on the management of agitation in the emergency situations. As more data becomes available on sedation of ABD further refinement of treatment, development of algorithms and protocols are possible[20]. In an

attempt to provide further data subsequent to the initial randomised control trial[28] this thesis addresses the key factors of the challenges in managing sedation of ABD.

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EVALUATION OF A SCORING SYSTEM FOR ASSESSING THE LEVEL OF AGITATION/SEDATION

BACKGROUND:

An agitation/sedation scoring system is important for the management of ABD because it can guide the specific treatments and ensure consistency of approach. The use of a score over time can document the degree of agitation as well as provide an assessment of the effectiveness of any initial sedation. It can therefore indicate the need for additional sedation or re-sedation in a consistent manner. A score that is rapidly and regularly recorded, rather than lengthy written documentation, allows a better assessment of the patient's response to sedative medication over time. The SAT (Sedation Assessment Tool)[1] is a simplified version of the altered mental status score (AMSS)[2]. Like the AMSS it assesses states of agitation and sedation but is simpler with only three scores above and below zero, and uses only two features for assessment of behaviour - responsiveness and speech.

AIMS:

The aim is to evaluate a simple scoring tool, the sedation assessment tool (SAT), for the assessment of agitation and sedation in patients with ABD by comparing it to the AMSS and determining if it is predictive of the requirement for re-sedation.

METHODS:

The study assessed a new scoring system, the sedation assessment tool (SAT), for agitation and sedation in patients with ABD during two study periods. To evaluate the SAT we compared scores in patients with ABD recruited to a clinical trial using the AMSS and converted these scores to the SAT. Plots of the AMSS and SAT versus time were visually inspected to compare trends in levels of agitation/sedation. To investigate if the SAT had the qualities to indicate the requirement for further sedation we undertook an analysis of the sensitivity and specificity of a rise in the score above zero to predict the administration of sedative medication in a prospective cohort of 138 patients. The duration of time to assessment for recording a score was measured by an independent observer and collected from ten health care workers involved in the management of patients with ABD. Inter-rater reliability was assessed getting two individuals to score the same patient at two different time points.

The SAT was evaluated in four different ways.

1. The AMSS and SAT were plotted against time for the three different arms of the clinical trial and compared by visual inspection.
2. The sensitivity and specificity were calculated for an increase in the SAT as a predictor of whether additional sedation was required to settle the patient.
3. The time each individual took to score patients were recorded and a median calculated to measure the likely time it took to score a patient using the SAT.

4. Inter-rater reliability was calculated for the overall 7 x 7 table of possible SAT scores from two raters.

OUTCOMES and CONTRIBUTION TO THE THESIS:

The SAT ensures that nursing staff document, monitor and assess the following:

- The SAT records the type and dose of medication used, the time given, and documentation of additional sedation and other medications administered at that time;
- The SAT ensures the sedating effect of the medication given is monitored and recorded every 10 minutes post injection, using an objective rating scale. This enables remote observation to occur when the patient is still highly agitated or aggressive, and/or is in seclusion, ensuring the safety of staff;
- The SAT ensures recording of adverse effects following Rapid Tranquilisation. This provides clinicians with a record to prevent future adverse events occurring;
- The SAT ensures monitoring of vital signs is done at 30 minutes post Rapid Tranquilisation; these are documented on the Standard Adult Observation Charts. Recording vital signs at 30 minutes post IM injection (when it is safe to do so), and half hourly thereafter is a requirement of HNE Mental Health.
- The SAT can be scored rapidly and guides interventions reliably and consistently.
- The SAT may also be useful as a clinical guide for future admissions in terms of providing historical data about which medication and dose achieved effective sedation, thus potentially reducing the risk of adverse events;
- The SAT provides a numerical score that is quickly and easily recorded rather than lengthy written documentation, this allows a better assessment of the patient's response to sedative medication over time, and can help determine the requirement for additional sedation.

Sedation Assessment Tool provides the clinician with information on the effect, time to sedation and the depth of sedation. The scoring of a patient's level of agitation and sedation alerts the staff to the level of distress which encourages the use of additional sedation to increase their comfort. The frequency of scoring the patients improves the monitoring of vital signs and recording the time and nature of adverse effects. It has an obvious practical application yet also can be used for the collection of data for research purposes. The SAT has been adopted by the Hunter New England Health District Mental Health in the clinical practice guidelines as the tool to assess the effect of sedation[3]. The

clinical practice guideline for management of ABD in the emergency department is currently under review and the SAT tool is incorporated in this document.

Acute Behavioural Disturbance Chart Report using the SAT

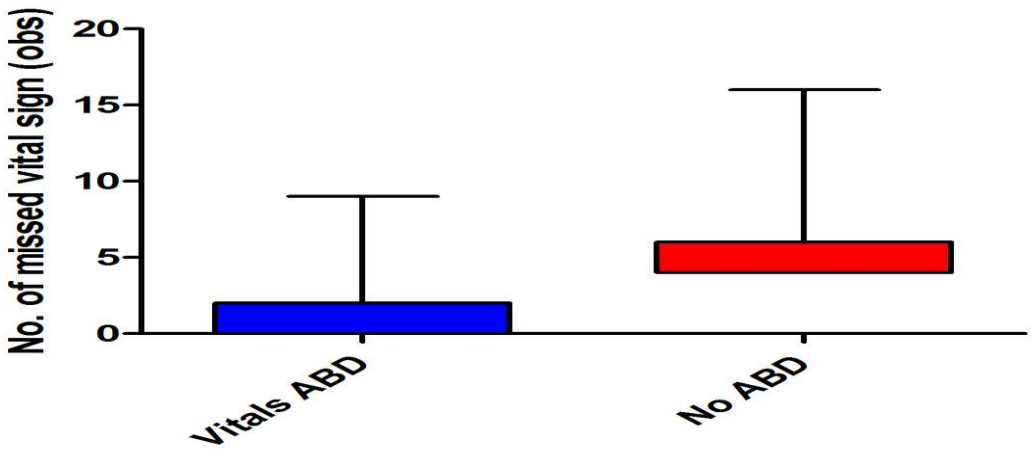
There is significant risk associated with managing episodes of ABD both for the patient and health-carers. An important aspect of management of these patients is the need to quickly and reliably assess their level of agitation and the therapeutic effects of any sedation given to the patient.

The ABD chart stems from the data sheet used in a randomised controlled trial of sedation in the Emergency department of the Calvary Mater Newcastle

The ABD chart provides:

- Inclusion and exclusion criteria: This provides the staff with prompts as to the appropriateness of giving parenteral sedation as a last option of treatment
- The Sedation Assessment Tool (SAT). This is a scoring system to assess the patient at baseline of the ABD and monitor the change in the level of aggression and depth of sedation over a short period of time. This provides a measure of the effectiveness of sedation and the time taken for sedation effect to occur. It can be scored rapidly and guides interventions reliably and consistently. This information can help determine the drug used for additional sedation attempts or for re-sedation at a later stage. It may also be useful for future admissions. It can therefore indicate the need for additional sedation or re-sedation in a consistent manner. A numerical score that is rapidly and regularly recorded, rather than lengthy written documentation, allows a better assessment of the patient's response to sedative medication over time
    - Adverse effects: A section to record adverse effects of the sedation. This provides clinicians with a record of whether the patient is likely to have an adverse event directly related to the agent given.
    - Guidelines and recommendations are included on the chart which directs treatment and encourages the use of additional sedation when the patient remains agitated.
    - Vital signs monitoring: After the administration of a sedating medication regular physical observations are required. Recording vital signs at 10 minutely intervals for the first hour, and half hourly thereafter is a requirement of the HNEMH guidelines (HNEMH Procedure 1.15.94_Seclusion.Oct 2008 P1-7) . An audit showed vital signs were less likely to be missed when the ABD chart was used.

Figure1: The frequency of missed vital signs when the ABD chart is used verses number of missed vital signs when the ABD chart is not used.



The Acute Behavioural Disturbance Chart has been used on approximately 200 patients with episodes of acute behavioural disturbance in the Psychiatric Intensive Care Unit (PICU) and the Psychiatric Emergency Care Centre (PECC). An audit of the specifics of the chart has been completed.

Results: The results auditing 15 charts with 9 criteria showed a compliance of 100% in 3 criteria (Name/Sign, Time and Medication sections). The sections least used were the restraint type 8/15 (53%) and the respiratory rate 9/15(60%).

Discussion: The information gained from the ABD chart for the HNE ethics approved audit of the sedation episodes, were presented at the HNEMH Grand Rounds March 2011. The findings included the median time to sedation and the frequency of additional sedation used and frequency of adverse events during the twelve month period. This data and information is un-attainable without the ABD chart.

Conclusions: The ABD chart is a chart to assess, record and monitor the effects of parenteral sedation given for the management of ABD in the mental health acute care settings. It provides the clinician with information on the effect, time to sedation and the depth of sedation. The ABD chart improves patient safety and comfort by increasing the frequency of monitoring vital signs and recording the time and nature of adverse effects. It is has an obvious practical application yet also can be used for research purposes with ethics approval.

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ORIGINAL RESEARCH

Sedation assessment tool to score acute behavioural disturbance in the emergency department

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Abstract

Objective: The objective of the study was to evaluate the effectiveness of the sedation assessment tool (SAT) in assessing patient response to treatment for acute behavioural disturbance (ABD).

Methods: The SAT is a simplified version of the altered mental status score (AMSS) and is a 7-point scale assessing levels of agitation and sedation using only two descriptors. To assess the SAT we firstly compared plots of the SAT and the AMSS versus time in patients with ABD recruited to a clinical trial. AMSS were converted to the SAT for this comparison. Second, the sensitivity and specificity were calculated for an increase in the SAT to +2 or +3 as a predictor of whether additional sedation was required in a prospective cohort of 138 patients. Third, interrater reliability was assessed using two individuals to score the same patient at two different time points and finally the time to record the score was measured.

Results: Plots of AMSS and SAT for 91 patients in the clinical trial illustrated similar trends in agitation/sedation. Seventeen of 138 patients in the second cohort had an increase in the SAT. Fifteen of 17 (88%) received additional sedation. The sensitivity and specificity of the SAT for additional sedation was 100% (95% CI 75–100%) and 98% (95% CI 94–100%), respectively. The median time for staff to assign the SAT was 10 s (range 3–15 s). Interrater reliability was high with a kappa of 0.87.

Conclusion: The SAT is a simple, rapid and useful measure of the level of agitation/sedation in patients with ABD. Increases in the score reliably indicated the need for further sedation.

Key words: *conscious sedation, emergency medicine, psychomotor agitation, scoring system, violence.*

Introduction

Acute behavioural disturbance (ABD) is a common problem in the ED, requiring rapid assessment and treatment.[1] There are significant risks associated with managing episodes of ABD, both for the patient and health carers. Well-defined clinical pathways of treatment will assist in this and should include a way to

monitor both the level of agitation and the level of sedation after medication is given. An agitation/sedation scoring system provides a method to do this and gives both a consistent approach and guides specific treatments, including initial and additional sedation.

Many scoring systems or tools are available for the assessment of agitation and sedation, but are predominantly designed to be used in the psychiatric or intensive care setting. A review of available scoring systems is provided to compare the features and attributes of the different tools used (Table 1). Scoring systems designed specifically for the mentally ill include the brief psychiatric rating scale (BPRS),[10] which does not contain items that specifically measure behavioural activity over a short time.[2] Scoring systems used in the critical care setting include the Richmond agitation sedation scale (RASS),[7] the overt agitation severity scale (OASS)[8] and the confusion assessment method (CAM-ICU).[13] However, these are designed to assess immobile, intubated patients and cannot be generalized to the ED setting where patients are initially highly mobile.

There are only a few scoring systems available for use in the ED assessing agitation/sedation or response to treatment with sedative medications. However, a number have been used in trials of sedative medications for ABD.[3,5,9,15,24] These include the altered mental status score (AMSS) and the behavioural activity rating scale (BARS).[2] The AMSS incorporates four descriptors and a reasonably complex 9-point scale. The BARS, having only one descriptor, is more subjective as it includes language, such as 'appears sedated', and uses a staff decision to restrain the patient physically, as part of the assessment of agitation.[2] A numerical score that is rapidly and regularly recorded, rather than lengthy written documentation, allows a more practical assessment of the patient's response to sedative medication.

We aimed to evaluate a simple scoring system, the sedation assessment tool (SAT), for the assessment of agitation and sedation in patients with ABD by comparing it with the AMSS[3] and determining whether it is predictive of the requirement for re-sedation.

Methods

Setting

The study was undertaken in the ED of a hospital with large number of patients with ABD. It is an urban ED with 27 000 annual presentations but admits approximately 5.2 per 1000 patients with ABD.[1] The hospital has a tertiary clinical toxicology and liaison psychiatry service as well as a medical inpatient drug and alcohol unit.

Study design

The study assessed a new scoring system, the SAT, for agitation and sedation in patients with ABD during two study periods. The first cohort of patients had the AMSS done prospectively as part of a clinical trial of sedative medications. The SAT was then scored retrospectively by simplifying the AMSS for each patient. The second cohort consisted of ABD patients where the SAT was done prospectively and its ability to predict the use of additional sedation was tested. The second cohort was also used to assess the interrater reliability and the time it took to record the SAT. Ethics approval was obtained from the local Human Research Ethics Committee.

Selection of participants

Both patient cohorts included adults who presented to the ED with ABD and who required parenteral sedation and physical restraint. In both cohorts patients could not be calmed with verbal de-escalation or oral medication. The first cohort of patients was recruited to a clinical trial of sedative medications for ABD from August 2008 to July 2009.[25] The ABD patients in the second cohort were routinely treated between August 2009 and June 2010 with a standardized sedation protocol incorporating the SAT.

Interventions

The AMSS is a 9-point scale (−4 to +4) that allows the assessment of both agitation using scores from +1 to +4 and sedation using scores from −1 to −4 (Table 2).[3] A score of 0 indicates the patient is neither agitated nor sedated. The AMSS therefore provides information on the degree of agitation and depth of sedation and can be used to measure the time to onset of sedation. We used it to assess level of agitation/sedation during a clinical trial.[25] However, both research staff and clinical staff found features of the AMSS difficult to use and that all four descriptors were not required to assess agitation and sedation. The scale was modified to produce the simpler SAT (Table 3), which is a 7-point scale with only two descriptors. The modification was done by combining scores of +2 and +3, and −2 and −3, into one

Table 1. Sedation scores currently available

Acronym	Name of score	Features	Agitation	Sedation	Applicable to ED
SAT	Sedation assessment tool	7-point scale (+3 to -3) 2 descriptors: responsiveness and speech	Yes	Yes	Yes
BARS[2]	Behavioural activity rating scale	7-point score (1–7) Only 1 descriptor only	Yes	Yes	Yes
AMSS[3]	Altered mental status score	9-point score (-4 to +4) 4 descriptors: responsiveness, speech, facial expression	Yes	Yes	Yes
RSS[4]	Sedation scale	6-point scale (1–6 'combative' to 'deep sleep') 1 descriptor only Only 2 levels of sedation	Yes	Yes limited	Yes
CS[5] AAS[6]	Combativeness scale	5-point score(1–5) of agitation 1 descriptor only, no sedation scale	Yes	No	Yes
RASS[7]	Acute arousal scale	6-point score (0–5) 1 descriptor only, no sedation scale	Yes	No	Yes
OAS[8]	Richmond agitation sedation scale	10-point score (+4 to -5) 2 descriptors 'Term' and 'description'	Yes	Yes	No – ICU
AS[9]	Overt aggressive scale	4-point scale of aggression 1 descriptor only, no sedation scale	Yes	No	Yes
BPRS[10]	Agitation scale	6-point agitation scale. 1 descriptor only, no sedation scale	Yes	No	Yes
OASS[11]	Brief psychiatric rating scale	7-point score (1–7) 24 descriptors	Yes	No	No – psychiatry
OAA/S[12]	Overt agitation severity scale	6-point scale (1–5) 47 descriptors with 12 sub-categories	Yes	No	No – ICU
	Observers assessment of alertness/sedation	4-point scale (1; deep sleep to 5; alert) 4 descriptors 'Responsiveness Speech Expression Eyes'	No	Yes	Yes
CAM-ICU[13]	Confusion assessment method	2-point scale (absent or present) 4 descriptors with sub-categories	Yes	Yes	No – ICU
PANSS[14]	Positive and negative syndrome scale	7-point scale (0; absent–6 extreme) Four 45 min clinical interviews.	No	Yes	No – psychiatric
RAS[15]	Ramsay assessment scale	6-point scale of sedation(1-6) 1 descriptor only	No	Yes	No – ICU
ABS[16]	Agitated behavioural scale	4-point scale (1–4 absent, slight, moderate, extreme) 14 criteria 3 underlying subscales	Yes	No	No – neuro ICU
AS[17]	Alertness scale	5-point scale alertness scale 8 visual and 12 auditory stimuli - 6 sounds and 6 words	No	Yes	No – anaesthesia
AVPU[18]	Alert, verbal, painful, unresponsive	4-point scale of responsiveness 1 descriptor only	No	Yes	Yes – neurological
GCS[19]	Glasgow Coma Scale	15-point score 3 descriptors: (eyes 1–4; motor 1–6; verbal 1–5)	No	Yes	Yes
FOUR[20]	Full outline of unresponsive score coma scale	20-point score 7 descriptors: (eyes 0–4; motor 0–4; brainstem 0–4; respiration 0–4)	No	Yes	No – ICU
ACDU[21]	Alert confused drowsy unresponsive	4 levels 1 descriptor only	No	Yes	No
CNS[22]	Grading of CNS stimulation	5 levels only 1 descriptor: relaxed to coma	Yes	No	Yes
MAAS[23]	Motor activity assessment scale	6 levels 1 complex descriptor	Yes	Yes	No

CNS, central nervous system.

Table 2. Altered mental status scale

Score	Responsiveness	Speech	Facial expression	Eyes
4	Combative, violent, out of control	Loud outbursts	Agitated	Normal
3	Very anxious, agitated	Loud outbursts	Agitated	Normal
2	Anxious, agitated	Loud outbursts	Normal	Normal
1	Anxious, restless	Normal	Normal	Normal
0	Responds easily to name, speaks in normal tone	Normal	Normal	Clear, no ptosis
-1	Lethargic response to name	Mild slowing and thickening	Mild relaxation	Glazed or mild ptosis < 1/2 eye
-2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis > 1/2 eye
-3	Responds only after mild prodding	Few recognizable words	Marked relaxation, slacked jaw	Glazed and marked ptosis > 1/2 eye
-4	Doesn't respond to mild prodding or shaking	Few recognizable words	Marked relaxation, slacked jaw	Glazed and marked ptosis > 1/2 eye

Table 3. Sedation assessment tool (SAT)

Score	Responsiveness	Speech
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious/restless	Normal/talkative
0	Awake and calm/cooperative	Speaks normally
-1	Asleep but rouses if name is called	Slurring or prominent slowing
-2	Responds to physical stimulation	Few recognizable words
-3	No response to stimulation	Nil

score making the SAT a 7-point scale (-3 to +3) such that +2 and +3 become +2, and +4 becomes +3, and similarly for negative scores. The four descriptors of the AMSS represented in the columns – 'responsiveness', 'speech', 'facial expression' and 'eyes' were reduced to two descriptors – 'responsiveness' and 'speech' as staff indicated they did not refer to the other two descriptors in their assessment. The response to sedation scores 0 to -3 were modified to be similar to the commonly used AVPU score (alert, verbal, painful, unresponsive) to increase consistency with other score systems used in the ED.[18]

The essential features of the SAT were the need for precise discriminating criteria with four of the following attributes:

1. Uses features specific for ABD patients in the ED assessing both agitation and sedation
2. Uses objective descriptors
3. Requires no patient participation; and
4. Has minimal need for training and provides ease of recall.

Data collection and processing

In patients recruited to the clinical trial the AMSS was scored at 5 min intervals for 20 min, and then half hourly until 2 h and then second hourly until 6 h. If any additional sedation was given the scoring interval of 5 min intervals was resumed to monitor the effects. From these AMSS values we derived the SAT score for every time point using the approach described above (i.e. scores of +2/+3 were converted to +2, and a score of +4 to +3, and similarly for negative scores).

Following the completion of the clinical trial a standardized sedation protocol was introduced into the ED and the new 7-point SAT was used for patients with ABD with the same timings for the scores. All scores from both periods were recorded in a spread sheet for analysis.

The time taken to assess patients with the SAT was measured by an independent observer (LC) and collected from 10 health-care workers involved in the management of patients with ABD.

The interrater reliability was evaluated by collecting independent scores from two staff members who simultaneously scored the patient using the SAT at the onset of the ABD and then re-scored the patient after 20 min had elapsed. The nurse responsible for the care of the patient routinely scores the patient at regular intervals as per the protocol guidelines. The nurse team leader is required to attend all ABDs in the department and was assigned as the second scorer to assess interrater reliability. Each staff scoring the SAT was blinded to the other score.

Primary data analysis

The SAT was evaluated in four different ways. To determine whether the AMSS provided any additional information on the level of agitation/sedation for patients in the first cohort with ABD compared with the SAT, the AMSS and SAT were plotted against time for the three different arms of the clinical trial and visually compared.

Second, the sensitivity and specificity were calculated for an increase in the SAT as a predictor of whether additional sedation was required to settle the patient. To do this the SAT scores for each patient episode of ABD were graphed against time to identify increases and decreases in the levels of agitation and sedation. For each patient episode the score was examined to determine whether a sudden increase in the score correlated with a patient receiving additional medication. An increase in the absolute score of +2 or greater from zero after the patient was settled for a minimum period of 1 h was defined as a patient having a repeat episode of ABD and determined to be a 'positive result' for the SAT. For example, a true positive was regarded as a rise in the score to a +2 or +3 that lead directly to the administration of additional sedative medication. Ninety-five per cent confidence intervals (95% CI) for the sensitivity and specificity were calculated using the Wilson procedure, including continuity correction.

Ten independent health-care workers were timed to see how long it took them to record an SAT. The times were recorded in seconds and a median calculated.

Interrater reliability was calculated for the overall 7 ¥ 7 table of possible SAT scores (-3 to +3) for 141 scores from two raters. The unweighted Cohen's kappa statistic of interrater agreement was calculated using StatsDirect v.2.7.0 (http://www.statsdirect.com) and the standard errors and 95% CI were calculated in Mathematica v.8.0.0 (http://www.wolfram.com) using the expression originally given by Fleiss *et al*.[26]

Graphical analysis was performed using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Ninety-one patients were included in the clinical trial and were randomized to three groups - 33 received droperidol alone, 29 received midazolam alone and 29 received the combination. Figure 1 compares the AMSS and SAT over time for the three groups, and shows that the trends of the two scores are similar for all three groups.

In the second cohort there were 138 patients who presented with ABD to the ED who required parenteral sedation and were scored using the SAT. Of the 138 patients, 17 had a recurrence of ABD after being initially sedated for a period of at least 1 h where the SAT increased to +2 or +3. Fifteen of the 17 (88%) received additional sedative medication. The sensitivity of the SAT to additional sedation was 100% (95% CI 75–100%) and the specificity was 98% (95% CI 94–100%). The positive predictive value was 89% and the negative predictive value was 100%.

The median time to score a patient using the SAT was 10 s (range 3–15 s) from 10 independent scorers in the ED. The interrater reliability was high with a kappa of 0.88 (95% CI 0.80–0.96) over all seven categories using two raters.

Discussion

The study suggests that the SAT is as effective at assessing the level of agitation and sedation as the AMSS but has the advantage of being less complex. The same changes in level of agitation and sedation over time were seen. An increase in the SAT score to +2 or +3 was a good predictor of the administration of additional medication. The ease of application and the practicality of the scale were demonstrated by the speed with which staff could assign a score for patients with ABD, despite the urgency and chaos of the ED setting.

A comparison of the SAT and AMSS versus time for the three different arms of the clinical trial indicates that the SAT shows the same temporal changes in the level of agitation and sedation as the AMSS. We suggest that the removal of two levels of scores and fewer features to observe resulted in little or no loss of information. This may be attributable to the inclusion of the

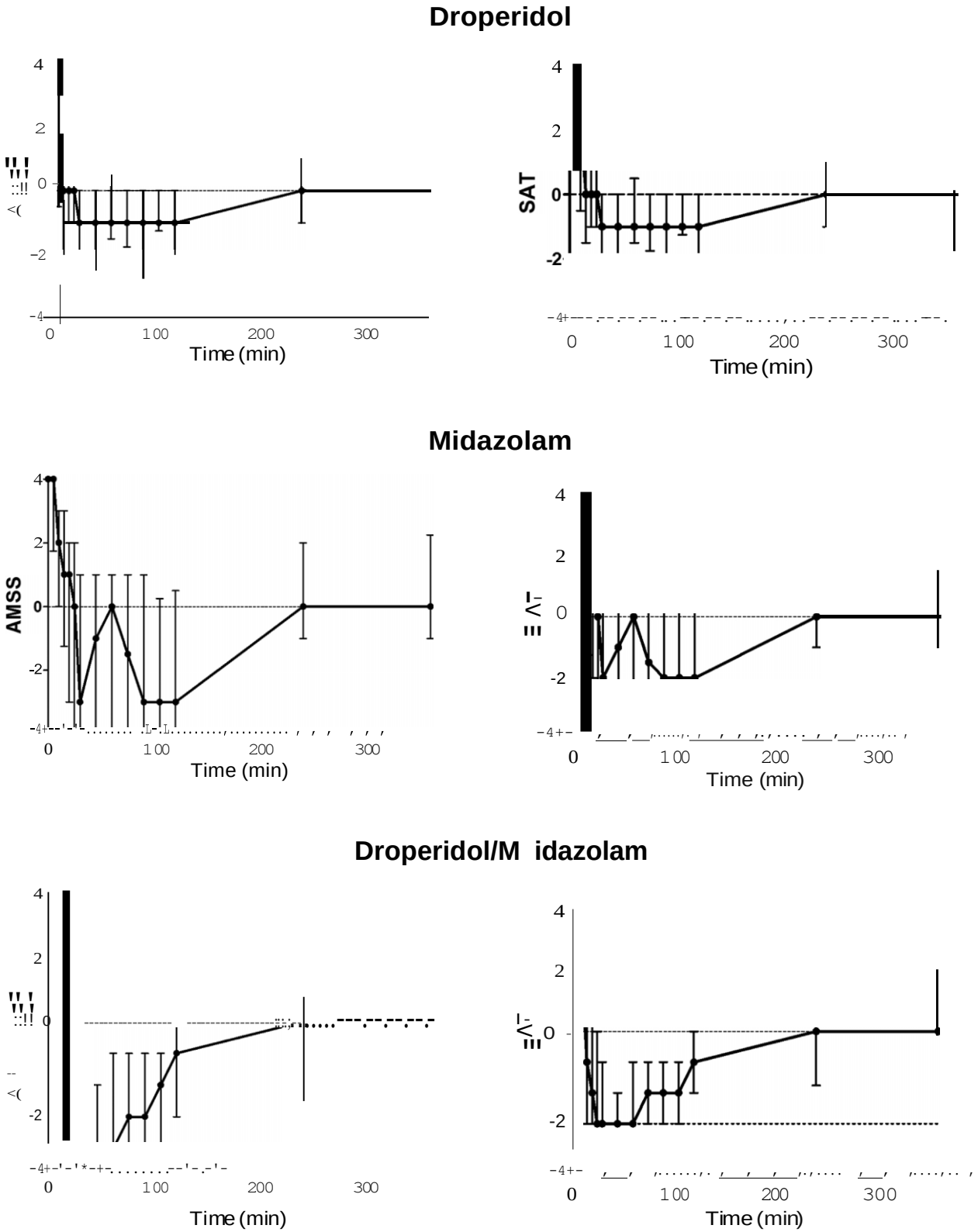

Figure 1. Comparison of the altered mental status score (Al\llSS) and sedation assessment tool (SAT) versus time for the three arms of the clinical trial.

more specific descriptors of agitation in the SAT.[5] The two retained descriptors – 'responsiveness' and 'speech' – are easily observed patient behaviours that are highly indicative of agitation and/or sedation, rather than more subtle and subjective signs, such as ptosis and facial expressions. In addition, the descriptor of 'responsiveness' for sedation was the same as that used for the AVPU score,[18] which is already well understood by ED staff.

We also suggest that the removal of two intermediate scores from the agitation and sedation parts of the scale reduces the effect of subjectivity. The responsiveness descriptors between levels +1 to +3 are 'Anxious, restless' (i), and 'Anxious and agitated' (ii), and 'Very anxious, agitated' (iii) (Table 1). These descriptors are very similar, resulting in staff experiencing difficulties in assigning a score. The difference between these levels (+1 and +3) did not appear to be clinically significant and did not impact on the measurement of responsiveness to treatment as seen in the scores plotted over time (Fig. 1).

The finding that the SAT provided an indication of the need to administer additional medication for sedation has demonstrated its usefulness and potential to improve patient outcomes. Of the numerous scoring systems available to assess agitation and sedation most provide limited information to assess the effectiveness of sedative medications, and if so do not necessarily relate to patient care delivery and patient outcomes (Table 1).

The short time it took to assess the patient using the SAT was a crucial factor for staff acceptance because busy ED staff will not use scoring systems unless they can be applied rapidly. In the evaluation of the RASS the investigators suggested that an acceptable time to assign a score was less than 20 s, which was indicated by compliance.[13] The CAM-ICU[27] assessment scale reported a mean time of 2–5 min as a measure of compliance of nursing staff, but it was introduced in the ICU setting, which is different from treating patients with ABD in the ED. The requirement for minimal training to use the SAT was essential because the ED has a high turnover of medical and nursing staff. The necessity for the SAT to be self-explanatory is essential as it might be the scorer's first encounter with it while they are simultaneously required to deal with the difficulties associated with ABD patients. Also the need to be able to score an agitated patient from a distance with no interaction or participation was a priority, because of the uncooperative nature and potential danger of these patients.

Even though a scoring system is validated and com- monly used, clinicians and researchers are constantly revising and modifying it to suit their needs. The fea- tures and characteristics of other commonly used scoring systems for the level of agitation and sedation are summarized in Table 1 together with their relevance to the ED. Most scores are designed for the intensive care or psychiatric setting, and only a limited number are relevant to the ED. Many of these scales use multiple descriptors, which can make assigning a score difficult if there is conflict between descriptors. The AMSS has four descriptors (each column) (Table 1), which can create a dilemma for the scorer because there might be an overlap between descriptors as to which level to rank them. For example, a patient might have marked ptosis but still be capable of loud abusive comments. There- fore, additional criteria, such as ptosis in the AMSS, have the potential to be more confusing for the scorer, making the score less reliable. Scoring systems that incorporate many descriptors might be not only time- consuming but create significant conflict for the scorer. In addition, facial expression and eye signs are not predictors of violence or in the definition of violence so are unlikely to add usefulness to a scale.[28]

Conversely, some scales oversimplify by using a single descriptor as a measure of agitation (Table 1).[5,6,8,9,15,22] An example is the 6-point agitation scale used by Knott *et al*., which ranks agitation on different levels from 5 to 0 using repetitive word descriptions of behaviour, such as 'highly aroused and violent', 'highly aroused', 'moderately aroused', 'mildly aroused'.[9] BARS includes the staff intervention of restraint, which is not an assessment of the patient's behaviour. The SAT, by using two simple descriptors of behaviours, is a compromise between single descriptor scales and those using multiple and often conflicting descriptors.

Another problem with many scoring systems is that they use either subjective descriptors open to interpre- tation or require specific training and experience to accurately assess the patient.[29] Facial expression is a good example of a subjective feature that might be difficult to interpret and is unlikely to help distinguish between levels of agitation compared with a description of 'verbal outbursts' or 'physical violence'. Subtle infor- mation gained from descriptors, such as facial expres- sion, might be reasonable in the research setting where trained observers are scoring and more detailed infor- mation is sometimes helpful. However, in the clinical setting a simpler score that uses objective and easily observed features is more practical.

A limitation in the evaluation of the SAT is that there is no gold standard with which to compare it. This is a problem in the validation of any scoring system. We visually compared the SAT with the AMSS, but the AMSS has not been formally evaluated except as a tool in assessing alcohol intoxication in which Miner *et al*. only used the responsiveness descriptor.[22] The AMSS is in fact a modified version of the BARS[2] with additional points from the observers assessment of alertness/sedation (OAA/S).[12] However, the merits of a scoring system may be better judged by its ability to meet the needs of the clinical setting and act as an objective research outcome.

Conclusion

The SAT appears to be a simple and clinically practical scoring system for assessing level of agitation and sedation. It can be scored rapidly and guide interventions readily and consistently. Using an objective method of assessment has many potential advantages for patients and staff.

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Competing interests

None declared.

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Chapter 3. A PILOT STUDY: Dexmedetomidine for Difficult to sedate patients with ABD

BACKGROUND:

A small number of aggressive or agitated patients are difficult to sedate, even after multiple doses of intramuscular (IM) or intravenous (IV) combinations of benzodiazepines and sedating antipsychotics, or are difficult to re-sedate after emerging with ongoing delirium. The difficulty in controlling these patients is disruptive to clinical care, time consuming and a dangerous management problem. Some patients are given large doses of multiple drugs, which can have a cumulative effect and may lead to prolonged sedation and/or over-sedation, or cause significant airway or cardiac complications. Numerous approaches have been attempted to manage and safely sedate these patients, including the use of barbiturates, propofol and opioids, but these remain unsatisfactory and there remains considerable risk to patient and staff.

Dexmedetomidine is a newer sedative agent that is in the same class as clonidine, a sedative and blood pressure medication that has been used for decades. Dexmedetomidine has been studied extensively as a sedative agent for agitated patients in the intensive care unit. It has been shown to be safe and effective, and it appears to have some advantages over midazolam as a first line agent. A recent study compared it to midazolam as a first line agent and showed that it was equally as effective as midazolam for sedating and had some advantages such as a reduced frequency of delirium[1]. Hypotension and bradycardia is common in this drug class of α_2 adrenoceptor agonists. Healthy volunteers had a consistent drop in heart rate when administered with large doses of dexmedetomidine [2]. Randomised controlled trials consistently report bradycardia and hypotension as a direct dose related effect of dexmedetomidine.[1, 3 4-6] . It has approval for use in Australia by the Therapeutic Drug Administration for the post-operative sedation of patients who have previously been intubated for a maximum of 24 hours[7]. Its use in the intensive care units is prevalent given its light sedative qualities and the ability of clinicians in this setting to titrate the infusion and give inotropes, bolus doses and bolus intravenous infusions as required.

AIMS:

This pilot study aimed is to investigate the use of dexmedetomidine in a small number of agitated patients in the emergency department. Although dexmedetomidine has had limited use in the emergency department and the medical wards, its effectiveness and safety in complex intensive care patients make it a good choice for further investigation in the sedation of agitated patients in other departments. One advantage is that it has a completely different pharmacological action to benzodiazepines, so may be effective in patients with substantial tolerance to benzodiazepines or other drugs which is a major issue in the patient group to be studied. The study allowed us to determine if dexmedetomidine is a safe and effective alternative sedative agent, so that we could then undertake an appropriately designed larger study to determine if it is a reasonable option in these patients. The goal was not only to investigate the effectiveness of intravenous (IV) dexmedetomidine in difficult to sedate patients with acute behavioural disturbance (ABD). Most importantly we needed to investigate the safety of IV dexmedetomidine as an infusion in non-intubated patients with ABD.

HYPOTHESES:

The specific hypotheses of the study were:

1. Dexmedetomidine is effective at sedating patients who have failed three previous attempts of sedation within a one hour period;

2. Dexmedetomidine will not cause respiratory compromise;

3. An infusion will be required to maintain sedation after the loading dose;

STUDY OUTCOMES:

Primary outcomes

To effectively sedate the patient (SAT of a score two less than baseline/or zero) during the administration of the loading dose and maintain sedation at a score of -2, rousable by physical stimuli) to zero (calm and alert) as per S.A.T.

Secondary outcomes:

1. To monitor the frequency of adverse effects i.e.; Airway obstruction, respiratory depression, bradycardia and hypotension

2. To monitor the frequency of intubation of the patient due to the need to resort to paralysis and sedation due to failed sedation.

OUTCOMES and CONTRIBUTION TO THE THESIS:

The opportunity of exploring an alternative agent was important given that no sedative can sedate all patients and the exceptional few who do not respond to antipsychotics or benzodiazepines are extremely problematic. With the role of dexmedetomidine evolving it was very valuable to investigate if it could be safely used under the controlled research setting. Given the volume of information published on the heamodynamic effects of dexmedetomidine, not only Intensive Care patients but also healthy volunteers, it is no surprise that this was a prevalent side effect in our pilot study in the emergency department. The ED patients required larger doses due to the light sedative characteristics of dexmedetomidine. This coupled with the noisy environment which is not conducive to sleep, renders the patient likely to be easily roused. The need to increase the rate of the infusion without the support of intensive care interventions called for the pilot study to be ceased on the grounds of patient safety. A study to reduce the incidence of heamodynamic adverse effects by using a protocol to limit the frequency of titration upward only succeeded in achieving less hypotension and did not reduce the incidence of bradycardia[8] Dexmedetomidine has been reported to cause pulseless electrical activity in vulnerable patients due to profound bradycardia and hypotension[9]. After several episodes of adverse effects the risk outweighed the benefit and the study ceased. The problem of how to sedate the most extreme and prolonged ABD without resorting to anesthetic agents remains.

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Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult-to-sedate acute behavioural disturbance

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ABSTRACT

Objectives To investigate the safety and effectiveness of dexmedetomidine for sedating patients in whom previous attempts at sedation in the emergency department have failed.

Methods A study was carried out on dexmedetomidine for sedation of patients with acute behavioural disturbance for whom at least two previous attempts at sedation with other drugs had failed. Either a loading dose of dexmedetomidine was administered or a loading dose then an infusion. Administration was titrated to the sedative effect and vital signs. The sedation assessment tool was used to assess effectiveness, and adverse effects were recorded. Effective sedation was defined as a fall in the sedation assessment tool by two levels or more for an hour or more.

Results A total of 13 patients were given dexmedetomidine. Five of the 13 had a loading dose only. Of these five, successful sedation was achieved in two, and the other three were only briefly sedated during the loading dose. One patient had hypotension. Eight patients received an infusion after the loading dose. Three were successfully sedated, but one developed hypotension. Four patients required a decrease in the infusion rate for hypotension, and in three of these the rate decrease compromised the sedation and one of these required intubation for sedation. The final patient had persistent acute behavioural disturbance, which required intubation for management. Five of the eight patients developed hypotension, and, of the five, one had bradycardia and one went into atrial fibrillation.

Conclusion Intravenous dexmedetomidine for difficult-to-sedate patients with acute behavioural disturbance is not safe in the emergency department setting.

INTRODUCTION

A small number of aggressive or agitated patients are difficult to sedate, even after multiple doses of intramuscular or intravenous combinations of benzodiazepines and sedating antipsychotics, or are difficult to resedate after emerging with ongoing delirium.[1] Trying to control these patients is disruptive to clinical care, time consuming and dangerous to staff and other patients. Numerous approaches have been attempted to manage and safely sedate these patients, including the use of barbiturates,[2] propofol[2] and ketamine.[3] However, these remain unsatisfactory, and there remains considerable risk to patient and staff, which often results in the patient requiring intubation, mechanical ventilation and admission to an intensive care unit (ICU).

Interest in the use of a_2-adrenoceptor agonists for sedation is increasing. The antihypertensive, clonidine, has been the most popular of these agents and has been used for decades for sedation in intensive care including control of opioid and alcohol withdrawal. However, it is long acting, and its use is often associated with rebound hypertension after discontinuation.[4] Dexmedetomidine is a newer sedative a_2-adrenoceptor agonist that is similar to clonidine, but has a shorter half-life, allowing sedation to wear off more rapidly, and has less effect on haemodynamics.[5] Dexmedetomidine has been shown to consistently reduce the use of opioids, propofol and benzodiazepines for sedation in the anaesthetic and ICU settings.[6] A major advantage of the a_2-adrenoceptor agonists is that they cause little or no respiratory compromise.[4–8] They also have a different pharmacological action from benzodiazepines, so may be effective in patients with substantial tolerance to benzodiazepines, which is another major problem in this group of difficult-to-sedate patients.

Dexmedetomidine has been studied extensively as a sedative and adjunct anaesthetic agent for patients in the ICU and operating theatres. It has been shown to be safe and effective, and it appears to have some advantages over midazolam as a first-line agent for sedation.[9 10] The results of two studies comparing dexmedetomidine with the commonly used benzodiazepines, lorazepam and midazolam,[9 11] demonstrated it to be a safe alternative in the ICU. Recent studies have also suggested that it is useful for procedural sedation.[7 8]

There is limited evidence available on the effective management of patients with acute behavioural disturbance (ABD) where standard approaches to sedation have not worked. Clinical practice guidelines do not cover the treatment options for managing repeatedly failed sedation. Current practice is to administer anaesthetic agents, which then requires the patient to be intubated and mechanically ventilated.[12] This option is a last resort, which is resource intensive and fraught with potential complications. No previous studies have explored an alternative management for failed sedation of ABD that does not require anaesthetic agents in the emergency department (ED).

The success of dexmedetomidine in ICU patients[9 11] and in anaesthetics[6 7] make it a good choice for investigation of the sedation of agitated patients in other settings. We hypothesised that

dexmedetomidine may be a safe and useful agent for the management of difficult-to-sedate patients in the ED. The aim of the study is to investigate the effectiveness and safety of dexmedetomidine in a small number of agitated patients in the ED.

METHODS

Study design

We undertook a study of dexmedetomidine for the sedation of difficult-to-sedate patients with ABD in the ED. The primary outcome was safety of dexmedetomidine, as determined by the occurrence of adverse effects. We aimed to recruit approximately 20 patients over a period of 18 months. The study was divided into two parts. In the first part, patients received a loading dose and then a repeat loading dose if required. In the second part, patients were administered a loading dose followed by a continuous intravenous infusion.

Setting

The study was undertaken from September 2009 to June 2011 in a tertiary teaching hospital with a large number of patients who had ABD and presented to the ED. It is an urban ED with 29 000 annual presentations, with about 6 per 1000 with ABD.[13] Ethics approval was obtained from the local human research ethics committee. Consent was waived because of the requirement for immediate treatment and patients' lack of decision-making capacity to consent to medical treatment being given as a duty of care.

Selection of participants and sample size

All adult patients (>18 years old) presenting to the ED with ABD were sedated according to a standardised protocol, which included physical restraint and an initial sedative antipsychotic, droperidol 10 mg, followed by a second 10 mg if the patient had not been sedated after 15 min. Those for whom at least two previous attempts at parenteral sedation had failed were considered for inclusion if they continued to score +2 or +3 on the sedation assessment tool (SAT) (table 1). Exclusion criteria were age <18 years, pregnancy, baseline systolic blood pressure (BP) <100 mm Hg, heart rate (HR) <60 beats/min, or a history of cardiac disease.

Interventions

Patients with ABD who were not sedated after at least two attempts with other parenteral drugs were identified by treating clinicians. The investigators were contacted as to suitability for recruitment to the study. All patients were placed in a resuscitation bay with cardiac monitoring, pulse oximetry and non-invasive BP monitoring. Two intravenous cannulas were inserted if not already in place for drug and fluid administration. All patients received a fluid load before dexmedetomidine.

For the first part of the study, a loading dose of dexmedetomidine (1 mg/kg up to a maximum of 100 mg) was given over 20–30 min. This could be repeated if the patient was initially sedated and then became agitated again. In the second part of the study, the loading dose could be followed by a second loading dose if necessary, and then a continuous infusion. The infusion rate was titrated to the level of sedation, as measured by the SAT and the patient's vital signs. The infusion was started at a rate of 0.7 mg/kg/h and could be titrated to effect between 0.2 mg/kg/h and 1.2 mg/kg/h in 0.1 mg increments.

Table 1 Sedation Assessment Tool: SAT

Score	Responsiveness	Speech	Scale
+3	Combative, violent, out of control	Continual loud outbursts	+1 to +3 Agitation
+2	Very anxious and agitated	Loud outbursts	
+1	Anxious/restless	Normal/talkative	
0	Awake and calm/cooperative	Speaks normally	Zero
-1	Asleep but rouses if name is called	Slurring or prominent slowing	-1 to -3 Sedation
-2	Responds to physical stimulation	Few recognisable words	
–3	No response to stimulation	Nil	

Data collection and processing

Data were recorded prospectively using a standardised chart developed for patients with ABD and then entered into a relational database. The following data were included for the study analysis: patient demographic characteristics (age, sex), cause of ABD, drugs given before dexmedetomidine (time of administration, drug-related adverse effects), dose and timing of dexmedetomidine, and injuries to patients and staff. Observations were recorded every 5 min until the sedation score remained at zero or less for >30 min and vital signs were stable. Observations included HR, BP, oxygen saturations and respiratory rate. All patients received an ECG when they settled.

The level of sedation was recorded using the SAT (table 1)[14] by emergency staff who were familiar with the SAT as part of a structured protocol for patients with ABD. The SAT was designed for rapid assessment of inpatients with ABD in the ED and evaluates both agitation and sedation on the same scale. The scale ranges from most agitated and combative (+3) to unconscious (-3).

If the patient failed to respond to dexmedetomidine, or developed any adverse effects, further intervention was decided by the treating clinician.

Outcome measures

The primary outcome was the frequency of adverse effects defined as the need for airway support, respiration rate <12 breaths/min, oxygen saturation <90%, hypotension (BP <90 mm Hg), bradycardia (HR <60 beats/min) and an unplanned ICU admission. The secondary outcome was effective sedation defined as a reduction in the SAT score from +2 or +3 by two levels or returning to zero (awake and cooperative), for a period of >1 h.

RESULTS

Over a period of 21 months, a total of 13 patients were given dexmedetomidine in the ED. All patients were administered with sedative antipsychotics, with or without a benzodiazepine before dexmedetomidine. The median age was 41 years (range 24–87 years). Two patients were over 80 years of age. Eleven patients were male. The cause of ABD was deliberate self-harm (six), alcohol withdrawal (two), recreational drug use (two), post-ictal delirium (one), hyperglycaemia (one) and acute psychosis (one).

There were five patients who only had the loading dose. Two had a repeat loading dose. Three patients were only briefly sedated during the period when the loading dose was being administered. Only one patient had an adverse effect: an 87-year-old patient who developed hypotension (systolic BP 85 mm Hg) (figure 1, table 2).

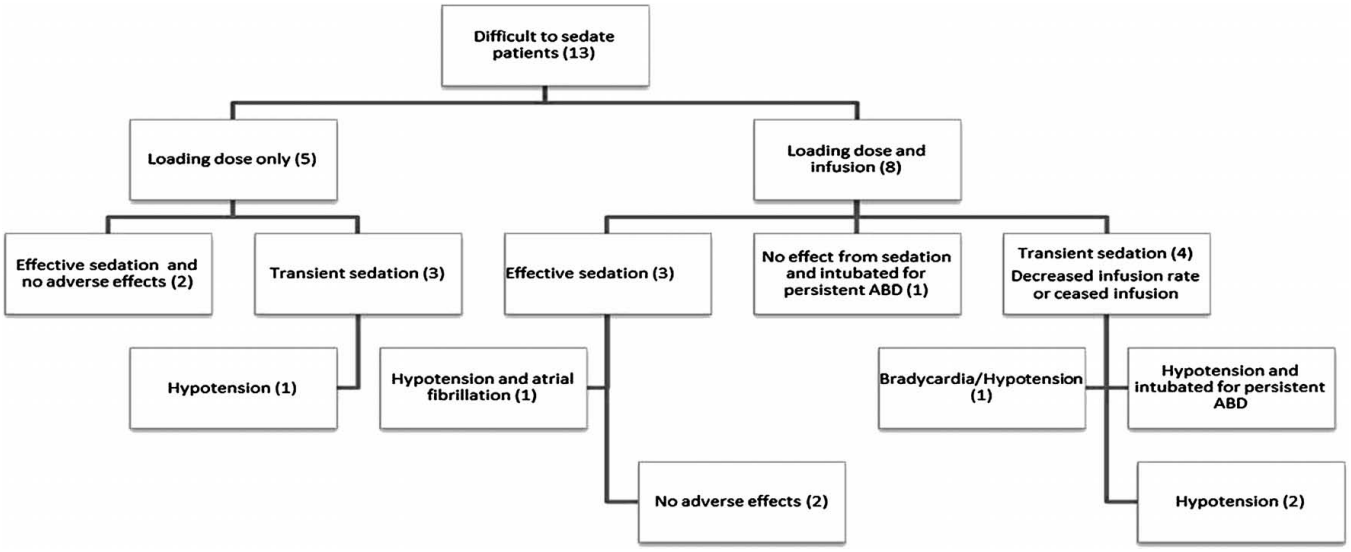

Figure 1 Flow diagram of the 13 patients recruited to the study. ABD, acute behavioural disturbance.

In the second part of the study, eight patients received an infusion after the loading dose (figure 1, table 2). Three were successfully sedated, and one of these developed hypotension. One patient had no response to dexmedetomidine and remained at a score of +2 to +3 and required intubation and anaesthesia. Four patients were transiently sedated, but then required a substantial decrease in the infusion rate to maintain a normal BP. In three of the four patients, the decrease in rate compromised the sedation effect. One of these subsequently required intubation for management of ABD. Five of the eight patients developed hypotension, and one of these developed bradycardia. One patient with persistent hypotension developed atrial fibrillation 7 h after the start of infusion, with evidence of first-degree heart block on an ECG before this. The study was ceased after the eighth patient with an infusion because of the frequency of patients developing hypotension.

The details of prior sedation and underlying cause of the ABD are outlined in table 1. Of the 13 patients, only five were successfully sedated. Four of these remained sedated for 6∈12 h (overnight), and none of these four had any adverse effects. Four patients were transferred to the ICU, two for closer monitoring and the two that failed sedation and required intubation. Of the remaining four, two were transferred to the psychiatric emergency care centre, and two remained in the ED with ongoing ABD. Both patients remained in physical restraints and were administered sedative agents intermittently with minimal effect.

No patient scored -3 (unconscious) on the SAT. The most common score was -1 (asleep but easily rousable) when sedation was achieved.

The most common adverse effect was hypotension, which occurred in six of the 13 patients. Five of these were during the administration of the infusion. Hypotension was managed by reducing the rate in three patients and ceasing the infusion in the other two (both older patients). Oxygen saturation and respiratory rate were maintained in all patients, and no patient had respiratory compromise.

DISCUSSION

Although the majority of patients with difficult-to-control ABD in the ED were initially sedated by dexmedetomidine, only four of 13 patients were effectively sedated for longer than an hour, without having any adverse effects (figure 1). The predominant adverse effect was hypotension in six patients. This failure of dexmedetomidine may have been due to the ED not being well

Table 2 Summary of the thirteen patients including the success of sedation and adverse effects

Age	Reason for presentation	Prior medication for sedation	Dexmedetomidine dose	Adverse effect	Sedation
41	Alcohol withdrawal	Diazepam 80 mg, Olanzapine 10 mg, Droperidol 30 mg	100 mg	Nil	Pass
86	Psychosis	Droperidol 20 mg	75 + 100 mg	Hypotension	Fail
27	DSP (quetiapine)	Droperidol 10 mg, Midazolam 20 mg	100 + 100 mg	Nil	Fail
45	Alcohol withdrawal	Droperidol 20 mg	100 mg	Nil	Fail
41	DSP (olanzapine)	Droperidol 20 mg	10 mg	Nil	Pass
87	DSP (bleach)	Clonidine 50 mg, Droperidol 10 mg	Stat 50 mg + infusion	Hypotension and bradycardia	Fail
46	Ketoacidosis	Droperidol 20 mg, Midazolam 15 mg	100 mg ¼ 100 mg + infusion	Intubation	Fail
32	Recreational drug misuse	Lorazepam 2 mg, Midazolam 20 mg, Droperidol 20 mg	100 mg + 100 mg + infusion	Nil	Pass
24	Post-ictal	Droperidol 10 mg, Midazolam 30 mg	100 mg + infusion	Nil	Fail
41	DSP (diazepam/ethanol)	Midazolam 30 mg, Droperidol 20 mg, Diazepam 20 gm	100 mg + infusion	Hypotension	Pass
34	Amphetamines	Droperidol 30 mg	100 mg ¼ infusion	Intubation	Fail
29	Threatened self-harm	Droperidol 20 mg	100 mg + infusion	Hypotension	Pass
40	Deliberate self-harm	Droperidol 30 mg	100 mg + infusion	Hypotension	Fail

DSP, deliberate self-poisoning.

enough equipped for managing the cardiovascular effects of dexmedetomidine.

The introduction of the infusion in the second part of the study was to determine if this improved the duration and therefore success of the sedation. The rapid onset and offset of the sedative effects of dexmedetomidine was clearly seen in three of the five patients given only a loading dose. These three patients became agitated again shortly after the loading dose was completed. We found that, with the introduction of an infusion, sedation was initially achieved in most of the patients (seven out of eight). However, the infusion rate in four of these patients was decreased substantially because of hypotension. Subsequently, the decrease in the infusion rate resulted in sedation wearing off in three of these patients.

Hypotension, bradycardia and atrial fibrillation have all been reported in larger ICU studies of dexmedetomidine.[11 15 16] The MENDS Study compared dexmedetomidine with lorazepam in 106 ventilated patients and reported atrial fibrillation in three patients given dexmedetomidine, but none given lorazepam.[9] Other studies of dexmedetomidine in anaesthetics and procedural sedation, as well as in healthy volunteers, have reported significant adverse cardiovascular effects,[4 5 7 9 17 18] and the occurrence and effects were thought to be related to the dose and infusion rate.[4 19 20] Studies in healthy volunteers report average decreases in the mean arterial pressure of 20–29% using recommended doses, [19 20] and a decrease of 18–23% in critically ill patients.[18 19] In a study of high-dose versus low-dose dexmedetomidine, there was no significant difference in the incidence of hypotension and bradycardia between dosing groups.[21] Hypotension was the most common adverse effect, occurring in 38% of patients. These patients had a dose increase more often than every 30 min and had more adjustments to their infusion rate.[21]

Bradycardia is commonly reported in previous studies. In a cohort of critically ill patients in the SEDCOM Study, bradycardia occurred in 42%[11] and in 16.5% in the DEXCOM Study.[16] In healthy volunteers in a dosing study, HR decreases of 16–20% were reported.[5] Correction of the bradycardia is recommended by administering atropine[19] and/or inotropes[17] to maintain haemodynamics within the predetermined limits.

In our study, the level of sedation and frequency of adverse effects were very sensitive to the infusion rate. The need for titration of the infusion rate plus the limited staffing and the busy nature of the ED may have contributed to the failure of dexmedetomidine. The increased infusion rate required to sedate patients with ABD resulted in hypotension. The study was ceased for safety reasons because of the frequency and severity of adverse effects.

Conclusion

Dexmedetomidine was able to initially sedate all but one patient for whom previous attempts at sedation in the ED had failed. However, the doses required to achieve the level of sedation required for ABD resulted in almost half of the patients developing hypotension. This frequency of adverse effects is beyond the monitoring capability of most busy EDs because of inadequate staff-to-patient ratios. Intravenous dexmedetomidine cannot be safely used for sedation of difficult-to-sedate patients with ABD in the ED.

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Competing interests None.

Ethics approval Ethics approval was provided by Hunter New England Area Health Service Human Research Ethics Committee.

Contributors LC helped design the study, coordinated recruitment and data collection, and drafted the manuscript. GKI helped design the study, recruited patients, reviewed all drafts of the manuscript, and takes responsibility for the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data is available to those interested.

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Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult-to-sedate acute behavioural disturbance

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Chapter 4: Investigation of the effects of droperidol on the QT interval using holter monitoring.

BACKGROUND:

Most patients who receive droperidol for sedation of ABD have an ECG tracing recorded post sedation routinely, as this is part of the standard monitoring. To further examine the cardiac effects of droperidol on these patients over time a 12-lead holter recorder and computer system with software to measure the QT interval at multiple time points is required. Currently, there is little data on QT interval changes following therapeutic droperidol administration using advanced holter recording. The holter monitoring is a similar procedure which is a compact version of the normal ECG recording and remains on the patient for a period of 4-24 hours as tolerated.

AIMS:

We aimed to accurately measure QT interval changes following the administration of 10 to 40mg of droperidol using continuous 12-lead holter recording.

HYPOTHESIS:

The specific hypotheses of the study are that:

1. There will be no significant detectable changes in the QT interval over time in patients administered with droperidol.
2. At the doses recommended in the Acute Behavioural Disturbance Protocol no QT changes will take place
3. No drug related arrhythmias will be detected.

The primary outcome was to detect a QT interval change over time post administration of droperidol. The secondary outcomes were to detect a dose relationship between QT interval changes and to detect any drug related arrhythmias.

METHODS:

Patients with acute behavioural disturbance were given an initial dose of 10mg droperidol intramuscularly followed by an additional dose of 10mg after 15min if required. The holter recorder was attached to the patients when the patient was settled. Continuous 12-lead holter recordings were then reviewed using proprietary Mortara software (Mortara, Inc. H-Scribe) to obtain high-resolution digital 12-lead ECGs which were then imported into E-scribe to obtain measure the QT interval. The H-Scribe System allows entry of patient information, review and editing of recorded data. Stored ECG data is downloaded for analysis to the H-Scribe System after the patient cable has been disconnected from the recorder. After the data is acquired at the H-Scribe System, The digital Holter recorder records 12-lead ECG continuously for up to 24 hours with the Compact Flash card. After the data is acquired via a card reader, the card is erased in preparation for the next recording.

Multiple recordings are stored on the hard drive of the H-Scribe System

The length of the QT interval was measured by the investigators using an overlapping view of the 12-leads with on screen calipers. For each ECG the QT interval was plotted against the heart rate (HR) on the QT nomogram to determine if it was abnormal. Each QT_HR pair will be plotted to determine if the QT interval is abnormal. For each case all QT-HR pairs will be plotted to determine if an abnormal QT occurs at any time. The frequency of abnormal QT intervals can then be calculated in the study group. Any arrhythmias, over the entirety of the recording were detected via the trend setting as part of the H-scribe software. 12-lead snap-shot ECGs were taken at set intervals for the study period and then loaded into E-Scribe. E-Scribe is a software program that automatically calculates the QT interval and displays this in a magnified view on a large screen with the chest and limb leads overlaid. On screen callipers were used to adjust the QT interval manually. The QT interval was recorded for each ECG as well as the heart rate (HR) to create a serial QT-HR dataset over time.

If the patient met the inclusion criteria of the DORM II observational study and required droperidol for sedation, they were given doses as per the treatment regimen. Following successful sedation, the patient was assessed by the nursing staff for compliance. If the patient is deemed calm/sedated a holter monitor was attached for as long as the patient tolerated it, or until completion of the study period.

OUTCOMES and CONTRIBUTION TO THE THESIS:

The same technique of detection using holter monitoring was used to detect QT prolongation in ziprasidone overdose[1] . Accurate measurement was necessary to resolve the uncertainty of measurement in-accuracy of the QT interval. Droperidol was not associated with QT prolongation when patients were excluded with co-morbidities and drugs known to cause QT prolongation. The results were presented at the International conference of Academic Emergency Medicine[2].

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- Droperidol is a highly effective sedative and anti-emetic agent.
- It has been removed or highly restricted because of concerns about QT prolongation and torsades de pointes.
- Outside of spontaneous reporting there is limited published evidence that droperidol causes QT prolongation.

WHAT THIS STUDY ADDS

- QT prolongation was associated with high dose droperidol for sedation in acute agitated patients.
- In patients with QT prolongation, this could be attributed to another drug or pre-existing cardiac disease in all cases.

AIMS

To investigate the QT interval after high dose droperidol using continuous 12-lead Holter recordings.

METHODS

This was a prospective study of patients given droperidol with a continuous Holter recording. Patients were recruited from the DORM II study which included patients with aggression presenting to the emergency department. Patients initially received 10 mg droperidol as part of a standardized sedation protocol. An additional 10 mg dose was given after 15 min if required and further doses at the clinical toxicologist's discretion. Continuous 12-lead Holter recordings were obtained for 2–24 h utilizing high resolution digital recordings with automated QT interval measurement. Electrocardiograms were extracted hourly from Holter recordings. The QT interval was plotted against heart rate (HR) on the QT nomogram to determine if it was abnormal. QT_cF (Fridericia's HR correction) was calculated and >500 ms was defined as abnormal.

RESULTS

Forty-six patients had Holter recordings after 10–40 mg droperidol and 316 QT–HR pairs were included. There were 32 abnormal QT measurements in four patients, three given 10 mg and one 20 mg. In three of the four patients QT_cF >500 ms but only in one taking methadone was the timing of QT_cF >500 ms consistent with droperidol dosing. Of the three other patients, one took amphetamines, one still had QT prolongation 24 h after droperidol and one took a lamotrigine overdose. No patient given >30 mg had a prolonged QT. There were no arrhythmias.

CONCLUSION

QT prolongation was observed with high dose droperidol. However, there was little evidence supporting droperidol being the cause and QT prolongation was more likely due to pre-existing conditions or

Introduction

Droperidol is a butyrophenone, antipsychotic medication that has been used extensively for decades to sedate patients with acute behavioural disturbance [1]. There have been concerns about the safety of droperidol because of its association with torsades des pointes (TdP) and QT prolongation [2]. Despite little evidence to support these claims [3], a black box warning was imposed by the United States Food and Drug Administration (FDA) in 2001 [3, 4] and other international drug regulatory bodies have removed it or restricted its use. This has led to a rapid decrease in its use and lack of availability [5].

Acute behavioural disturbance is common in the emergency department and often manifests as violence and aggression. Such behaviours put both staff and patients at risk of harm and can result in damage to property and injury [6]. Patients who cannot be settled by verbal de-escalation methods or oral sedation require mechanical restraint and parenteral sedation [7]. There is increasing evidence that droperidol is an effective drug for rapid sedation and it appears to be safer than benzodiazepines, because the latter cause over-sedation and require more additional sedation [8–11]. The increasing evidence for the benefit of droperidol [8–11] and the long safety record prior to the black box warning [12] means that there needs to be a reassessment of its safety so that a potentially beneficial drug is not restricted without good reason.

Although a number of studies have reported the association between droperidol and QT prolongation [13], they have not used standardized approaches to measuring the QT interval or have used Bazett's formula for heart rate (HR) correction, which over-corrects with heart rates greater than 70 beats min^{-1} [14]. There is limited information on electrocardiogram (ECG) changes following the administration of high dose droperidol for sedating agitated patients. Such studies have used a limited number of 12-lead ECGs [8, 9, 15]. A better understanding of the ECG changes following large doses of droperidol is required to provide a better assessment of the risk of QT prolongation and TdP in this setting.

The aim of this study was to investigate the cardiac effects of droperidol by accurately measuring the QT interval after the administration of droperidol using high resolution continuous 12-lead Holter recordings and assessing the risk of TdP using the QT nomogram [16].

Methods

This was a prospective study of patients given droperidol, which used high resolution Holter recordings to investigate the effect of high dose droperidol on the ECG and in particular, its effect on the QT interval. Patients were recruited as part of the DORM II study. DORM II is an observational study of patients with aggression or agitation presenting to the emergency department requiring parenteral sedation and physical restraint. Ethics approval was obtained from the local Human Research Ethics Committee. Due to the lack of decision making capacity in these patients and a duty of care to sedate them, patient consent was waived by the ethics committee.

Patients were included in this study between September 2009 and June 2011 from one hospital emergency department site involved in the DORM II study where there was access to Holter recordings. This was an urban emergency department with 30 000 annual presentations and approximately 5.5 presentations per 1000 with violence and/or agitation requiring parenteral sedation.

The DORM II study recruits adult patients (>16 years of age) presenting to the emergency department with violence and/or agitation who do not settle with verbal de-escalation or the administration of oral medication. A standardized intramuscular sedation protocol is followed for all patients, including routine observations (heart rate [HR], blood pressure [BP], respiratory rate [RR] and pulse oximetry) [6, 8] and the sedation assessment tool (SAT) to monitor agitation and sedation [17]. All patients are initially administered 10 mg intramuscular droperidol and if they do not settle within 15 min they are given a second dose of 10 mg. If patients still do not settle 30 min after their initial assessment, further sedation with droperidol is determined by the clinical toxicologist.

A purpose-designed chart was completed for all patients in the DORM II study, including observations, treatments and adverse effects. Once the patient was settled they had an ECG done and in this study were assessed by the nursing staff for suitability for a Holter recording. Patients were recruited if they were settled enough for a Holter recorder and its 12 leads to be attached, and the patient was able to tolerate this for at least 2 h. The duration of recording was for as long as the patient tolerated the Holter leads, until the patient was discharged or transferred, or 24 h had passed (maximum length of the digital Holter recording). Patients were excluded if they were not in sinus rhythm. The following data were included for the study: age, gender, drugs taken prior to droperidol and the dose and timing of droperidol.

For each admission 12-lead ECGs were extracted from the digital Holter recordings as follows. The H12+24 Hour Digital Holter Recorder (Mortara, Inc.) records a continuous 12-lead ECG onto a 24 h compact flash card. Continuous 12-lead Holter recording data were then acquired via a card reader and downloaded to a desktop computer using proprietary software (H-Scribe; Mortara, Inc.). The software allows the continuous 12-lead recordings to be stored and reviewed. The trend setting was used to determine if any arrhythmias had occurred and then high resolution digital 12-lead ECGs were extracted from the Holter recordings using H-Scribe. A 10 s 12-lead ECG was extracted every hour from the recording. The 12-lead ECGs were imported into E-scribe (Mortara, Inc.) to measure the QT interval. The

E-Scribe software includes an algorithm to measure automatically the QT interval which includes averaging over multiple beats in each lead. It then displays the computer measured QT in a magnified view with the six chest and six limb leads separately overlayed, an overlay or butterfly view. On screen callipers are provided to adjust manually the QT interval if required. The measurement of the QT interval was reviewed by a clinical pharmacologist/toxicologist with expertise in the measurement and assessment of the QT. The QT interval was recorded for each ECG as well as the HR. Each QT interval measurement was plotted against the HR on the QT nomogram [16, 18]. Any QT–HR pair that was above the line on the QT nomogram was defined as abnormal. QT_cF (Fridericia's HR correction of the QT interval) was also calculated and a cut-off of 500 ms was defined as abnormal.

The primary outcome for this study was the proportion of patients who had any QT–HR pairs above the 'at risk' line on the QT nomogram [16]. Secondary outcomes included $QT_cF > 500$ ms and arrhythmias occurring after the administration of droperidol. Medians, ranges and interquartile ranges (IQR) are reported for continuous variables. Graphical analyses were done in GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego, California, USA, http://www.graphpad.com.

Results

There were forty-six patient admissions, 33 males and 13 females with a median age of 34 years (IQR 25 to 41 years, range 17 to 85 years) included in the study from which 3 to 23 12-lead ECGs were obtained for each admission. Three patients were excluded, two with chronic atrial fibrillation and one with left bundle branch block. Two patients had a second recording on a separate admission. Twenty-nine patients received 10 mg droperidol, 11 received 20 mg, three received 30 mg and three received 40 mg. The Holter recording was commenced a median of 60 min (IQR 38 to 111 min, range 16 to 307 min) after the first administration of droperidol. The median duration of the recordings was 6 h (range 2 to 24 h). A total of 316 QT–HR pairs were included and 284 QT–HR pairs were below the 'at risk line on the QT nomogram (Figure 1). Thirty-two QT–HR pairs in four patients were above the 'at risk' line (Figure 2). The QT_cF was greater than 500 ms in three of the four patients (three male patients, Table 1). Figure 3 shows the time course of QT_cF after the administration of droperidol. None of six patients who received 30 or 40 mg droperidol had an abnormal QT. No patient had an arrhythmia and TdP did not occur in the four patients with prolonged QT intervals.

Details of the four patients with a prolonged QT are included in Table 1. The first patient presented to the emergency department with hallucinations after using amphetamines. He was a regular illicit intravenous drug user and a carrier of hepatitis C. His urine drug screen was positive for amphetamines and tetrahydrocannibinol. The Holter monitor was placed 1 h after droperidol 10 mg and the QT was normal until it became prolonged 11 h after droperidol (Figure 3, blue line). The second patient had been on methadone for 6 months and an ECG obtained prior to methadone commencing was normal. He was given 20 mg droperidol and the Holter placed 50 min after this. The QT interval was prolonged from the start until the end of the Holter recording 7.5 h after droperidol (Figure 3, red line). The third patient was a homeless intravenous drug user who attempted suicide using liquid petroleum gas inhalation. The Holter was placed 2.25 h after droperidol was administered. QT prolongation appeared 4.33 h after droperidol was administered and remained prolonged on discharge the next morning. However, the QT_cF remained less than 500 ms except for on ECG record-

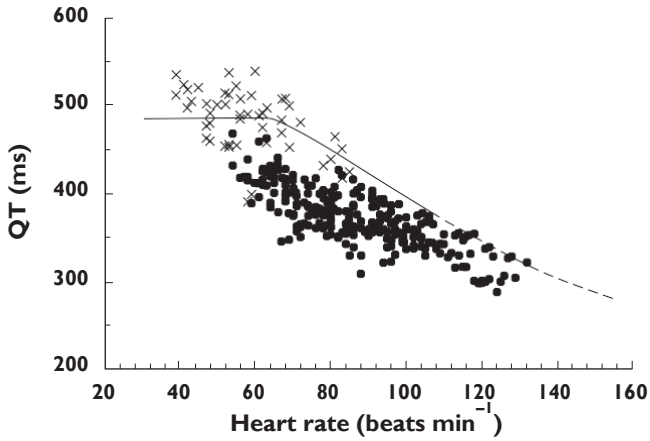

Figure 1

Plot of the QT interval *vs*. heart rate for the 42 patient admissions where the QT was normal. ●, normal QT; ×, abnormal QT

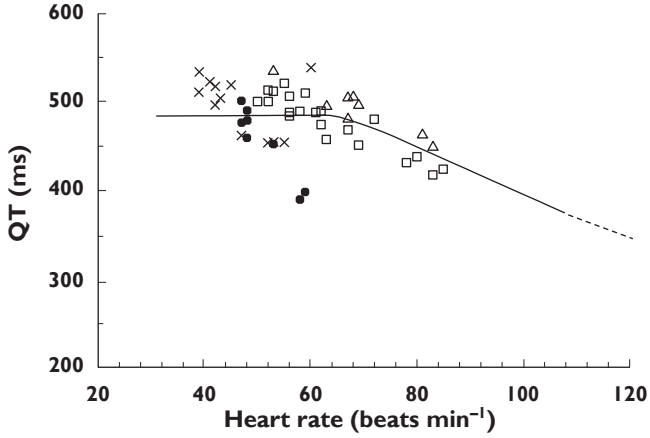

Figure 2

Plot of the QT interval *vs*. heart rate for the four patients with an abnormal QT interval (see Table 1) ×, 52M patients □, 41M patient; △ 25M patient; ●, 17F patient

Table 1

Details of the four patients with QT prolongation

Age/ gender	Dose (mg)	Reason for presentation	History	Time to QT prolongation (min)	Maximum QT interval (ms)	Heart rate (beats min^{-1})
41 M	10	Hallucinations due to amphetamines	Poly-substance abuse. Urine drug screen positive for amphetamines and THC	210	522	53
25 M	20	Amphetamine toxicity and agitation	Taking methadone confirmed on urine drug screen.	50 (start of recording)	512	59
52 M	10	Attempted suicide with liquid petroleum gas	Poly-substance abuse. Urine drug screen positive for THC, amphetamines	260	534	39
17 F	10	Lamotrigine overdose	Post-natal depression	110 (start of recording)	505	40

THC, tetrahydrocannibinol.

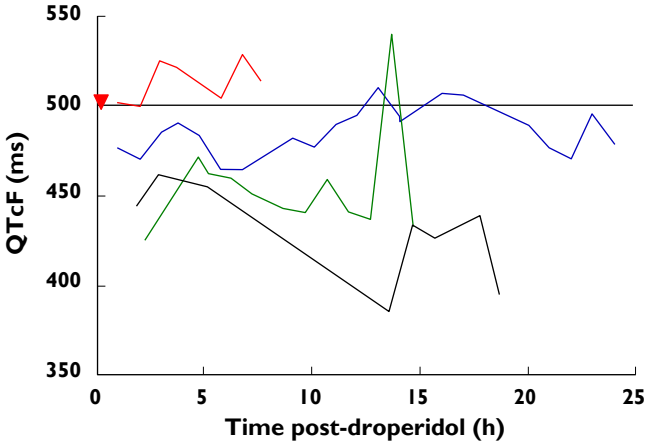

Figure 3

Plot of the QT_cF *vs.* time for the four patients with an abnormal QT, 41M patient; 52M patient; 25M patient; 17F patient; ▼, repeat droperidol dose

ing 13.66 h post-droperidol (Figure 3, green line). The patient also remained bradycardic on discharge and never had a HR greater than 60 beats min^{-1}. Despite repeated attempts the patient could not be contacted for cardiology follow-up. The fourth patient was female with post-natal depression who took an overdose of 2800 mg lamotrigine. The Holter was placed 1 h and 50 min after droperidol was administered. The QT interval was prolonged from the start of the Holter recording and resolved over several hours. She was also bradycardic and had a HR less than 60 beats min^{-1} for the duration. Her QT_cF remained less than 500 ms for the duration.

Discussion

QT prolongation occurred in four patients after high dose droperidol administration and in these patients with an abnormal QT, there was little evidence to support droperidol being the cause. In at least one of the four patients with an abnormal QT, another drug was more likely to be the cause (methadone treatment). In addition, there was no dose dependence with droperidol and the QT prolongation, because QT prolongation occurred in three patients given 10 mg and one given 20 mg and there was no QT prolongation in patients given larger doses. The study used accurate measurement of the QT interval and a previously evaluated approach to determining abnormal QT intervals associated with TdP [18]. By employing continuous recording over many hours we were able to determine when the QT prolongation occurred in relation to the droperidol dose using QT_cF (Figure 3). This intensive sampling in the first few hours after droperidol administration also meant we did not rely on one or two ECGs, or single lead ECG recordings. Importantly, no arrhythmias occurred including those who had a prolonged QT interval.

In the four patients with abnormal QT intervals, the QT prolongation could reasonably be attributed to other drugs or a pre-existing condition (e.g. undiagnosed cardiac condition). Two males with an abnormal QT were taking therapeutic drugs known to prolong the QT interval (methadone) or taking illicit drugs (e.g. amphetamines) (Table 1). The female patient presented with a large lamotrigine overdose and had a prolonged QT on the QT nomogram from the time the Holter was commenced. Lamotrigine has been shown to inhibit the human cardiac delayed rectifier potassium current *in vitro* and may be associated with QT prolongation [19]. This patient had a slow heart rate and the QT_cF was never greater than 500 ms (Figure 3). The other male patient with poly-substance abuse had unresolved QT prolongation and bradycardia on discharge and was lost to cardiology follow-up. Such factors as undiagnosed pre-existing cardiac disease or other drugs are substantial confounders in this patient cohort who presented to the ED with agitation and violence. However, it is not possible to exclude droperidol completely as a contributing factor in these four patients.

The change in QT_cF over time, shown in Figure 3, also provides some insight into whether the abnormal QT was due to droperidol. The patient on methadone (25-year-old male, Figure 3) clearly had an abnormal QT_cF for the duration of the Holter recording. However, for the other two

male patients, the QT_cF was only abnormal between 12 and 18 h after droperidol, not consistent with the expected pharmacokinetics of droperidol.

This study used accurate measurement of the QT interval [20] and a previously evaluated approach to determining abnormal QT intervals [16, 18]. Two early studies prior to the black box warning issued by the FDA suggested that QT prolongation occurred with high dose droperidol [13, 21]. However, in both studies there were problems with QT measurement and the heart rate correction of the QT interval, and both studies were done in patients under general anaesthesia. A more recent study of patients undergoing general anaesthesia found that similar numbers of patients had QT prolongation if they were given normal saline or droperidol [22]. The first of the two earlier studies by Guy *et al*. [21] provided no information on the method of measuring the QT and used the mean of the QT from different leads, which provides a biased estimate of the QT interval [23]. Lischke *et al*. used an automatic measurement from a standard ECG machine and also used the mean of the QT from different leads [13]. Both studies used Bazett's formula to correct for HR which is known to overcorrect in patients with HRs faster than 70 beats min^{-1} [24, 25]. This may account for the unusual finding by Lischke *et al*. that the mean maximal QT prolongation occurred within 1 min of drug administration, at the same time as a significant increase in HR. In addition, the rapid rise and fall of the QT_c in the study by Lischke *et al*. is not consistent with the known slow adaptation of the QT interval to sudden or rapid changes in HR due to QT hysteresis [26]. A more recent study by Charbit *et al*. suggested there was a significant change in the QT_cB (Bazett's) following droperidol (compared with ondansetron). However, they showed rather erratic changes in the QT_cB commencing minutes after the administration of droperidol, which did not account for inter-individual variation in HR correction or QT hysteresis, making these results difficult to interpret [27].

In our study the QT nomogram was the major method used to determine if the QT was abnormal [18]. The QT nomogram provides a different approach to assessing whether a QT interval is abnormal because the QT is plotted against the HR avoiding the need for HR correction formulae. However, it is not possibly to plot easily the QT–HR pair *vs*. time to determine if the abnormal QT coincides with the dosing of droperidol. We therefore used QT_cF to explore this relationship in the patients with an abnormal QT, despite QT_cF being a population based HR correction formula which can be problematic for fast and slow HRs [16].

The use of automated measurement of the QT interval using standard ECG machines is known to be inaccurate [14, 28]. In this study we used an automated QT measurement in dedicated software for the measurement of QT which also allowed the use of on-screen magnifi and callipers for manual checking of the QT measurement by a clinician experienced in reading ECGs [14]. This approach provided the most accurate method of QT measurement and the application of this in a clinical setting is unique to the study.

A limitation of this study was the variability of the commencement time of the continuous Holter recordings. This was determined by the time to sedation but in 75% of the patients the Holter was commenced within 2 h. The compliance of the patients was imperative and was difficult to predict. Another problem was that the study did not include patients where it was unsafe or not possible to put on the Holter recording device. However, this was rare and was unlikely to have biased the patient group included in the study.

The absence of baseline ECGs is also a limitation of the study but it is not possible and unsafe to attempt to record an ECG or Holter in violent and agitated patients. There is limited data on the underlying frequency of QT prolongation in this population of patients presenting with acute behavioural disturbance. Three previous studies of droperidol in this population found no signifi difference between patients given another drug for sedation (midazolam or olanzapine) *vs.* patients given droperidol [8, 9, 15]. In the DORM study there was no difference in the number of patients with an abnormal QT with two of 31 given 10 mg droperidol, two of 29 given 10 mg midazolam and four of 29 given 5 mg midazolam and 5 mg droperidol [8]. In another study where droperidol was compared with olanzapine or control, in patients already receiving midazolam, the median QT_cB (Bazett's) intervals in 211 patients having an ECG did not differ between groups and was between 440 ms and 450 ms. One patient given olanzapine and one patient in the control group (midazolam alone) had QT_cB measurements of 500 ms and 512 ms respectively. These studies suggest that there is a larger proportion of patients in this population who have an abnormal QT_cB, with a higher median of 440 to 450 ms [15] compared with normal populations of 410 to 420 ms [29] and a greater number of outliers [8, 15]. The number of patients in our study with an abnormal QT on the Holter is consistent with this. Studies in other populations have also found that QT prolongation is often present in a proportion of patients prior to the administration of droperidol. In a study comparing droperidol and ondansetron for postoperative nausea and vomiting, 21% of patients had a long QT_cB pre-operatively before any drug was administered [30].

Although QT prolongation was observed with high dose droperidol in this study, there was little evidence to support droperidol being the cause and QT prolongation was more likely to be due to pre-existing conditions or other drugs. There was also no evidence of dose dependence in cases where QT prolongation occurred.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

(available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. GKI is supported by an NHMRC Clinical Career Development Award ID 605817.

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Chapter 5: Sedation of acute Behaviour disturbance in the geriatric population

BACKGROUND

Acute behavioural disturbance (ABD) in the elderly is an emergency which carries considerable additional risk. It occurs frequently in hospitalized patients and is reported to occur at a rate of 10%-40% in hospitalised elderly patients [1]and commonly occurs in the emergency department[2] The additional difficulties the elderly add to treating ABD is their unknown and known medical background as well as the possibility of drug-drug interactions [3]. Agitation in the elderly most often stems from delirium and/or dementia, and less commonly from Alzheimer's disease and late–life psychosis [4-7]. Most of these patients settle with the many strategies and techniques used to calm, orientate and settle their disturbed behaviours. Failing this parenteral medication is sometimes un-avoidable in order to manage the risk and cease the interruption of attaining a diagnosis and delivery of essential care [5, 8]. There is no consensus what is the best agents and dose for sedating agitated elderly ED patients[6]. There are many studies published concerning the presentation, prevention, prevalence and assessment of the elderly who present to the ED with symptoms of delirium and other altered mental states[8-11]. There are several other studies evaluating the long term management of agitation[12, 13] but there is little evidence based literature to guide the pharmacological treatment of acute agitation in this vulnerable patient population[4, 14]. There is no treatment approved by the United States Food and Drug Administration for the treatment of agitation in delirium [8, 11]. Literature supports the current belief that neuroleptics are superior to benzodiazepines in the treatment of delirium in the elderly [3, 4, 11, 15] as benzodiazepines are known to cause un-wanted side effects such as delirium , excessive sedation, increased risk of falls, respiratory compromise and behaviour dis-inhibition[4, 7, 16-18]. Lorazepam remains the only benzodiazepine commonly recommended in the elderly for ABD[17 19, 20] and is the only benzodiazepine used in a randomized controlled trial in older patients with agitation[21]. This multicentre trial by Meehan et al. conducted in the psychiatric setting compared lorazepam to a placebo and olanzapine and used two hours as the time point for sedation which questions the severity of the agitation. Since the development of the newer antipsychotics many are managed using these, although no double blind placebo trial exists to provide the evidence of effectiveness[1]. Haloperidol is considered the drug of choice for the elderly experiencing ABD[4, 16], yet the FDA has not approved any drug for behavioural agitation in dementia[6, 16] and in 2008 haloperidol received a black box warning (BBW)[22] and is associated with QT prolongation and torsades de pointes (TdP)in elderly patients. The options of atypical antipsychotics have been associated with an increased mortality rate in the elderly[5, 23] and a black box warning has been issued by the FDA on olanzapine regarding increased mortality with dementia related psychosis[24]. Additionally olanzapine cannot be administered within two hours of a benzodiazepine [25]. It remains unclear not only what are the best agents to be most effective and safe but also what dose is most appropriate for sedating the

elderly, despite the clinical burden[6, 14, 26] and the clinicians choice often relies on anecdotal evidence and individual preference.

All recommendations suggest low doses for the elderly[3, 19, 27], Many guidelines recommend small and half doses of typical and atypical antipsychotics with or without lorazepam[17, 19, 28]. The goal is to only administer the minimum dose required[14]. In severely disturbed patients some may require higher doses of intramuscular injections in the patient with acute distress [29, 30]. This is rarely reported yet the incidence of presentations in the EDs of ABD in the elderly population is readily occurring and likely to become more frequent with our aging population[2]. Yet most of the recommendations are referring to chronic treatment of agitation, with daily dosing regimens in the elderly not ABD as an emergency in the ED.

The emergency department setting commonly has patients presenting with ABD of un-known origin. There are no published trials to study sedation of the elderly in the ED with undifferentiated diagnosis[31]. Guidelines are numerous giving indications for choice of drugs specific to different conditions. Alexopoulos et al describes prescriptive recommendations for the use of antipsychotics in the elderly and states over twenty different conditions specific to each drug choice [32]. This information is not translatable to the ED where the diagnosis is mostly unknown. In acute agitation in the ED parenteral sedation has to be effective across all diagnostic categories regardless of the etiology of the aggression[33].

The dilemma of treating the ABD safely and effectively whilst considering the potential adverse drug effects is complicated by the elderly's increased co-morbidities and likely poly-pharmacy. A rate of adverse effects from other trials of sedation for ABD in the ED of predominantly younger populations ranging from an adverse event rate of 13%, 15% and 19% respectively comparing antipsychotics and benzodiazepines[34-36]. The expert consensus guidelines [15] prefer benzodiazepines in preference to antipsychotics in those patients who have poor cardiac function. Meagher states the choice of a drug and dose of sedative is determined by the route, patients age, the degree of agitation and the risk of developing side effects[37]. These determinants are difficult to assess in a busy emergency department with an acutely violent patient.

AIM

To determine if the protocol for ABD using droperidol for the treatment of ABD was appropriate to use on the elderly in the emergency department.

OUTCOME AND CONTRIBUTION TO THE THESIS:

The relevance of this patient cohort to this thesis is the controversy which reigns over the possible QT prolongation effects of droperidol. Geriatric patients are a very difficult group complicated by the fact that there is even greater concern that droperidol will cause cardiac toxicity. Overall there is a lack of high quality clinical evidence surrounding the effectiveness and safety of drugs used for rapid sedation of violent and aggressive elderly patients. There appears to be a gap in what the guidelines are recommending and what is clinical practice. When caution with dosing is exercised in an attempt to avoid adverse drug effects it is reasonable to expect the need for additional sedation. However there exists a difficult balance between prolonging the ABD or failing to control violent behaviour and the risk of adverse drug effects.

Droperidol is a useful drug in the acute setting initially when the patients are obstructive to assessment and are at risk of falling due to their aggression from confusion, or when they are refusing treatments or investigations in order to get a diagnosis. Subsequently other oral drugs and strategies need to be considered for regular management. Due to this study of the elderly we continue to use the droperidol sedation protocol in the emergency department but use increments of droperidol 5mg rather than 10 mg initially as additional sedation can be given incrementally if required. Droperidol has since been added to the Calvary mater sedation guidelines for sedation of the elderly.

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Brief Report

Parenteral sedation of elderly patients with acute behavioral disturbance in the ED☆,☆☆,★

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a r t i c l e i n f o

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a b s t r a c t

Purposes: This study aimed to investigate sedation of elderly patients with acute behavioral disturbance (ABD) in the emergency department (ED), specifically the safety and effectiveness of droperidol.

Basic Procedures: This was a prospective study of elderly patients (≥65 years) with ABD requiring parenteral sedation and physical restraint in the ED. Patients were treated with a standardized sedation protocol that included droperidol. Drug administration, time to sedation, additional sedation, and adverse effects were recorded. *Effective sedation* was defined as a drop in the sedation assessment tool score by 2 or a score of zero or less.

Main Findings: There were 49 patients with median age of 81 years (range, 65-93 years); 33 were males. Thirty patients were given 10 mg droperidol, 15 were given 5 mg droperidol, 2 were given 2.5 mg, and 2 were given midazolam. Median time to sedation for patients receiving 10 mg droperidol was 30 minutes (interquartile range, 18-40 minutes), compared with 21 minutes (interquartile range, 10-55 minutes; $P = .55$) for patients receiving 5 mg droperidol. Three patients were not sedated within 120 minutes. Eighteen patients required additional sedation—10 of 30 (33%; 95% confidence interval, 18%-53%) given droperidol 10 mg compared with 7 of 15 (47%; 95% confidence interval, 22%-73%) given 5 mg. Fourteen patients required resedation. Adverse effects occurred in 5 patients (hypotension [2], oversedation [2], hypotension/oversedation [1])—2 of 30 given 10 mg droperidol and 3 of 19 not treated according to protocol. Midazolam was given initially or for additional sedation in 2 of 5 adverse effects. No patient had QT prolongation.

Principal Conclusions: Droperidol was effective for sedation in most elderly patients with ABD, and adverse effects were uncommon. An initial 5-mg dose appears prudent with the expectation that many will require another dose.

1. Introduction

Acute behavioral disturbance (ABD) in the elderly is a difficult management problem in the emergency department (ED). In addition to the difficulties with treating any patient with ABD, there is a higher incidence of comorbidity in elderly patients, including them being on multiple medications [1]. Most elderly patients with ABD settle with various strategies used to calm, orientate, and settle disturbed behavior. However, a small number remain at risk to themselves and/or others and require parenteral sedation and physical restraint to ensure the safety of the patient and staff [2].

It remains unclear what the best agents are for parenteral sedation of ABD in the elderly [3] and if a dose reduction is required [4]. There are no studies of ABD in elderly ED patients [5], and there is no specific drug therapy approved by the United States Food and Drug

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Administration (FDA) [2]. Although the literature supports the current preference for antipsychotics over benzodiazepines [6-8], there are no trials supporting this. Establishing an effective and safe medication for parenteral sedation of the elderly is essential for providing rapid diagnosis and treatment of the underlying delirium or other cause for agitation and aggression.

Recently, we have shown that droperidol as a single agent is effective in sedation of adult patients in the ED and was safer than benzodiazepines [9]. As part of an ongoing study of sedation in the ED, we investigated the use of droperidol for sedation of elderly patients with ABD.

2. Methods

This was a prospective observational study of elderly patients (N65 years of age) recruited as part of the DORM II study. DORM II is an observational study of patients with ABD presenting to an ED and requiring parenteral sedation and physical restraint. Ethics approval was obtained from the local human research ethics committee. Consent was waived because of the requirement for immediate treatment and the patients' lack of decision-making capacity to consent to medical treatment being given as a duty of care.

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SCORE	RESPONSIVENESS	SPEECH
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious and restless	Normal
0	Responds easily to name, speaks in normal tone	Normal
-1	Responds only if name is called loudly	Slurring or prominent slowing
-2	Physical stimulation	Few recognisable words
-3	No response to stimulation	Nil

Fig. 1. Sedation assessment tool used to assess the level of agitation and sedation in patients with acute behavioral disturbance.

All adult patients (≥18 years of age) who present to the ED with ABD are recruited to DORM II if they do not calm with verbal de-escalation or oral medication and require parenteral sedation and physical restraint. All patients are then treated according to a standardized intramuscular sedation and observation protocol in a critical care area [9,10]. Heart rate (HR), blood pressure (BP), pulse oximetry, and respiratory rate are recorded every 5 minutes for 20 minutes and thence every 30 minutes. Agitation and sedation are assessed using the sedation assessment tool (SAT) (Fig. 1) [11]. The SAT score allows rapid assessment before and after sedative medication. The treatment protocol recommends an initial intramuscular dose of 10 mg droperidol, followed by a second dose of 10 mg if they are not sedated after 15 minutes. Patients not settling after 30 minutes must be discussed with the on call clinical toxicologist to determine any further sedation [12].

An ABD chart is used to record all observations, adverse effects, and treatments that the patient receives. All patients have an electrocardiogram (ECG) done if possible once settled. The QT interval is manually measured on all 12-lead ECGs, using a previously developed method [13]. QT-HR pairs from each ECG are plotted on the QT nomogram to determine if the QT is abnormal [14]. All information from the ABD chart and additional information from the medical record (eg, medication chart) is entered into a relational database, including demographics, medication used, sedation scores, clinical observations, QT interval, and adverse effects.

We reviewed all ED patients with ABD who were 65 years and older from the DORM II database from August 2008 to August 2012. The following information was extracted: demographics, medication (time of dose, dose, and additional sedation), time to sedation defined as a fall in the SAT score by 2 levels or a score of zero or less, failed sedation defined as not settling within 2 hours based on SAT scores, the proportion of patients requiring resedation after initially settling for at least 1 hour, and adverse drug effects (respiratory rate ≤12 breaths per minute, systolic BP ≤90 mm Hg, HR ≤60 beats per minute, oxygen saturation ≤90, extrapyramidal side effects, or QT prolongation).

Medians, ranges, and interquartile ranges (IQRs) are reported for continuous variables. Percentages are reported for dichotomous outcomes with 95% confidence intervals (CIs). Statistical and graphical analyses were done in GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA; www.graphpad.com).

3. Results

There were 49 patients with a median age of 81 years (range, 65-93 years; IQR, 71-85 years), and 33 were males (67%). Of 49 patients, 30 (61%) were treated according to the recommended protocol and were initially administered 10 mg droperidol. Seventeen patients were given less than the dose of droperidol recommended by the protocol—5 mg (15) and 2.5 mg (2). Two other patients varied from the recommended drug protocol and were given midazolam (2.5 and 5 mg). Of the 49 patients, 34 had an ABD chart with the time to sedation completed, 22 of 30 receiving 10 mg droperidol, 10 of 15 receiving 5 mg droperidol, and the 2 receiving midazolam.

Three patients were not sedated within 2 hours. One patient was given 10 mg droperidol, 1 was given 5 mg droperidol, and a third was given 2.5 mg midazolam. In those patients who were sedated, the median time to sedation in 21 of 30 receiving 10 mg droperidol was 30 minutes (IQR, 18-40 minutes; range, 5-60 minutes), which compared with a median time to sedation of 21 minutes (IQR, 10-55 minutes; range, 5-108 minutes; $P = .55$ Mann-Whitney U test) in 9 of 15 patients receiving 5 mg droperidol (Fig. 2). The patient who received 5 mg midazolam took 50 minutes to sedate. Time to sedation was not recorded in 15 patients.

Eighteen patients (37%) required additional sedation (Fig. 3), including 10 of 30 patients (33%; 95% CI, 18%-53%) given 10 mg droperidol compared with 7 of 15 patients (47%; 95% CI, 22%-73%) given 5 mg droperidol initially. One patient initially given 2.5 mg midazolam required additional sedation. Fourteen patients (29%) required resedation more than 1 hour after their initial sedation, 9 receiving 10 mg droperidol initially, 3 receiving 5 mg droperidol initially, 1 receiving 2.5 mg droperidol, and 1 receiving midazolam.

Adverse effects occurred in 5 patients (10%)—hypotension (2), oversedation (2), and hypotension with oversedation (1) (Table). One patient who developed hypotension (10 mg droperidol) had a myocardial infarction 12 hours after droperidol and died 2 weeks later. He was 75 years old with preexisting severe cardiac disease. Of 30 patients given 10 mg droperidol alone, 2 (7%; 95% CI, 12%-24%) developed adverse effects compared with 3 of 19 patients (16%; 95% CI, 4%-40%) who were not treated according to the sedation protocol

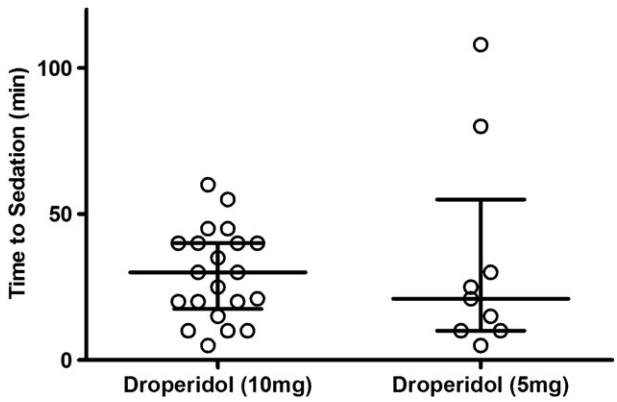

Fig. 2. Time to sedation for patients receiving 10 mg droperidol (n = 21) vs patients receiving 5 mg droperidol (n = 9).

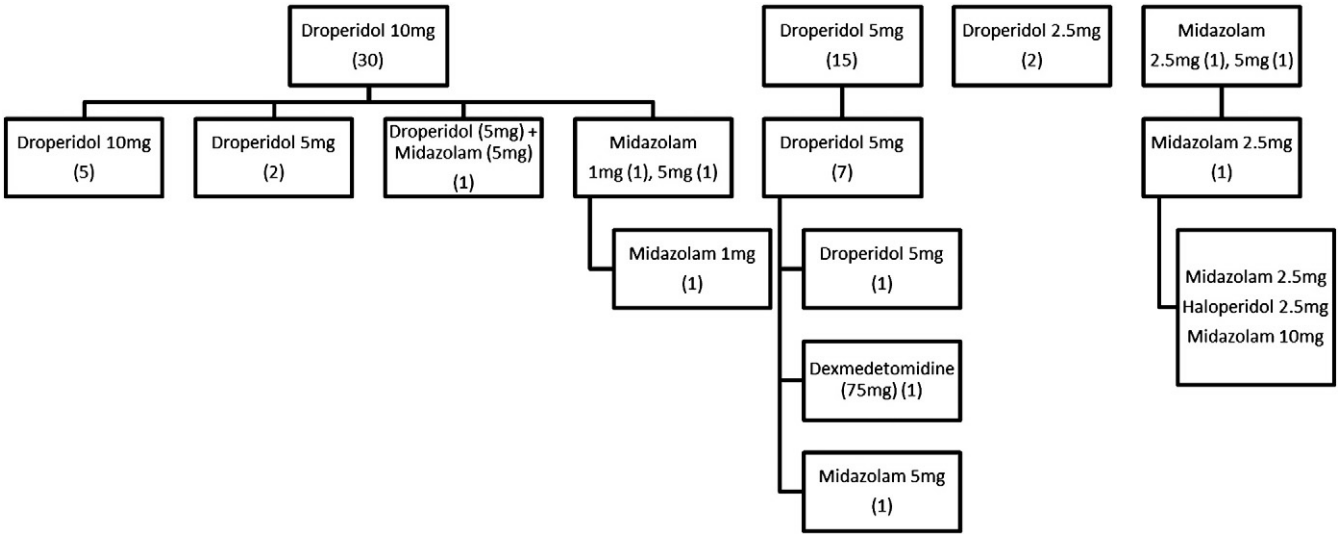

Fig. 3. Flow chart of the dose and drug used for initial and additional sedation.

(Table). Midazolam was administered to 5 patients on 10 occasions for initial or additional sedation. It was administered on a further 6 patients on 9 occasions for resedation. Midazolam was associated with 2 of the 5 adverse effects (Table), 1 patient given an initial dose and then further doses of midazolam and 1 given midazolam for additional sedation after droperidol. Electrocardiograms were obtained in 22 patients after droperidol, and no patient had QT prolongation (Fig. 4). There were no extrapyramidal side effects.

4. Discussion

This study shows that administering doses of 5 to 20 mg of droperidol was effective in sedating most elderly patients in the ED with ABD. The time to sedation was similar for patients initially given 5 mg compared with those given 10 mg. However, patients given an initial dose of 5 mg were more likely to require an additional dose of droperidol to achieve sedation. Overall, 37 (76%) of the 49 patients were given a total of 10mg or more droperidol to initially achieve effective sedation (Figs. 2 and 3). Adverse effects were uncommon but appeared to be more common with a larger initial dose of droperidol and/or in combination with midazolam.

The study supports an initial lower or half dose of droperidol in the elderly with ABD, in line with previous reviews and guidelines [15-17]. However, further doses may need to be given after 15 minutes if the patient is not sedated [4,18]. Incremental dosing gives the clinician the advantage of being able to judge the clinical effect over time, which is particularly useful in the elderly who have significant comorbidities.

Traditionally, haloperidol has been used as the first-line drug for the treatment of ABD in the elderly [19]. It is thought to be safer than other drugs because it causes less sedation and respiratory depression and has minimal effects on BP [20]. However, there are advantages to sedation in acutely agitated patients because it makes it easier to properly assess the patient and investigate underlying causes for the ABD [21]. Droperidol is more sedating than haloperidol, with a more rapid onset of action [8], and has been shown to be effective for sedation of adult patients with ABD in the ED [9,22,23].

Droperidol was issued with a black box warning by the FDA in 2001 because of concerns about QT prolongation and torsades de pointes (TdP) [24]. However, a systematic review was unable to identify published cases of droperidol definitely causing TdP [25], and the spontaneous reports to the FDA provided no clear evidence of an association between droperidol, TdP, and death [26]. Before 2001, droperidol was used for decades specifically for severely agitated behavior and physical aggression with a good safety record [27]. There remains significant controversy in the literature regarding the validity of the evidence and if the FDA warning was warranted [25,26,28]. Our study suggests that droperidol is safe in the elderly with no cases of QT prolongation on ECGs collected after droperidol administration (Fig. 4). Haloperidol was issued with a black box warning in 2007 with good evidence that it is associated with TdP [29].

Table
Description of the adverse drug reactions, including the time of the reaction and the time and type of additional sedation administered.

Sex Age	Initial drug (dose, mg)	Adverse effect		Additional sedation	
		Type	Time (min)[a]	Time (min)[a]	Drug (dose, mg)
M 75	Droperidol (10)	Hypotension	30	Nil	-
F 68	Droperidol (10)	Hypotension	5	Nil	-
M 73	Droperidol (10)	Airway obstruction	100	40	Midazolam (10)
F 87	Droperidol (2.5)	Oversedation	480	270	Droperidol (2.5)
M 66	Midazolam (2.5)	Hypotension and oversedation	65/480	49-360	Midazolam (28) + haloperidol (2.5)

[a] Time of adverse reaction or administration of additional sedation after the study drug was administered.

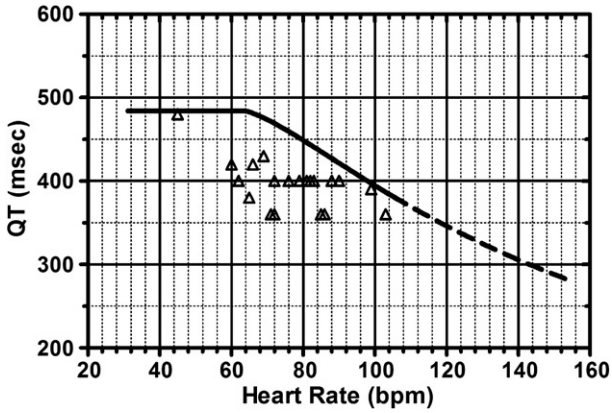

Fig. 4. Plot of QT vs HR for 22 patients given droperidol 10 mg.

Adverse effects occurred in 10% of patients, which is similar to studies of sedation in younger adult populations in the ED, which report adverse effects in 13% to 19% of patients [9,30,31]. One 75-year-old male patient had an acute myocardial infarction 12 hours after 10 mg droperidol. He developed hypotension 30 minutes after being given droperidol, but the patient had a significant cardiac history, and multiple factors were likely to be responsible for the poor outcome.

Midazolam was administered to 11 patients for initial, additional, or resedation, despite it not being recommended as part of the DORM II protocol. It appeared to contribute to 2 of the 5 patients with adverse effects. This supports concerns with the use of benzodiazepines in the elderly [6,7] because they are known to cause delirium, excessive sedation, increased risk of falls, respiratory compromise, and behavioral disinhibition [16,19].

All drugs used for rapid sedation are associated with adverse effects, and their use should always be a balance of the benefits in sedating patients with ABD vs the risks. Adverse effects occurred in 2 patients given 10 mg droperidol alone and in another given 10 mg droperidol followed by midazolam (Table). This would suggest that a lower dose of 5 mg initially may be the better option.

5. Conclusion

The study has shown that 5 to 10 mg of droperidol is effective for sedating elderly patients in the ED with ABD. Adverse effects were uncommon and no more common than previous studies of adult populations. They appeared to occur with larger doses of droperidol and with midazolam alone or in combination with droperidol. A reasonable approach to sedating elderly patients with ABD would be to commence with 5 mg droperidol with the expectation that repeat doses will be required in almost half of patients.

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Chapter 6 : Prospective study of sedation of ABD in the psychiatric setting

BACKGROUND

There is a direct relationship between mental illness and violence[1, 2]. In addition there is evidence of a higher incidence of violence and aggression when major mental illness and disorder are coupled with substance abuse or dependence, the highest being attributable to people with a personality disorder and co-occurring substance use problems[2-4] When it is deemed necessary to given parenteral medication for ABD it is generally accepted that poly-pharmacy should be avoided and medication doses ideally should be as low as possible to decrease the associated risk of adverse effects[5, 6]. However the necessity to administer above the recommended dosages in acute distress is recognized and accepted practice[6] Overall there is a lack of empirical evidence surrounding the effectiveness and safety of drugs used for rapid tranquilisation due to the ethical issues and the need to obtain consent. Many trials require written consent and require co-operation from the patients prior to recruitment in the form of performing tests such as ECGs and obtaining samples[7, 8] and many use a placebo as a comparator[9, 10] which is impossible when treating the most acutely agitated patients. Therefore unfortunately most trials within the mental health care setting do not represent persons in the most highly agitated states which is normally clinically encountered. Reporting of adverse effects is rarely documented in the literature because drug trials in the acute psychiatric setting predominantly have outcomes focused on level of aggression. This is evidenced by the use of scales such as the Global Clinical Impressions-Severity scale and Overt Agitation Severity Scale[11] , or sleep[12] reported as the primary outcome. A trial in Brazil[11] comparing five different drugs in various combinations reported excessive sedation in 70% of patients in one arm of the study, but respiratory rate or oxygen saturation was not reported and only blood pressure was recorded at hourly intervals. This focus on behavioural outcomes as a measure, together with the inability to have close access to the patient due to seclusion, makes the recording of vital signs and detection of adverse effects more infrequent in the mental health care setting and therefore there is likely under-reporting of the actual risk associated.

In contrast the emergency department is continuously monitoring and recording vital signs. Thomas considered vital signs a priority and were recorded with the sedation assessments at 5, 10,15, 30 and 60 minute intervals[13]. Knott and Thomas were diligent with regular observations of vital signs and the discussion of the results reflected the importance of these outcomes in the choice of sedation recommended. In the haloperidol verses droperidol trial 8 of 68(12%) had hypotension overall[14]. The droperidol verses midazolam trial had 21 of the 74 patients (28%) as this study included oxygen saturation and respiratory rate in the observation set[13]. The Martel et al study monitored vital signs every

15 minutes in the initial hour and reported 21 out of the 144 patients with respiratory depression [15]. In the lorazepam verses droperidol trial[16] the vital signs were monitored frequently within the first sixty minutes period but only reported at the sixty minute interval as an outcome. Nobay et al monitored vital signs every 15 minutes in the RCT of lorazepam, haloperidol and Midazolam[17].

Due to the success of the DORM project (Midazolam versus Droperidol) in acute behavioural disturbance in the emergency department[18], the Hunter New England Mental Health Centres' medicines committee has made a recommendation to use Droperidol for sedation within the institution. The mental health centre has a totally different patient population. The agitated mental health cohort of patients suffering from psychosis, as opposed to delirium, is complicated by the fact that many mentally ill patients are routinely prescribed the same class of drug as droperidol. The regular use of a different antipsychotic (haloperidol) in the psychiatric setting for the treatment of acute behavioural disturbance has been questioned. This needed to be evaluated for safety and effectiveness as it is criticised on the grounds of being less sedative and is associated with multiple side effects. Use of droperidol in the Mental Health Hospital (ICU /admissions unit) escalated following the original DORM RCT. This was based on the results of the trial initially and subsequently became standard practise due to its effectiveness. This is contrary to the guidelines and recommendation of all Mental Health Policies. We studied a 12 month period of sedation practice in the psychiatric intensive care unit to understand current practice prior to commencing of a randomised controlled trial to determine the effectiveness of droperidol for sedation in the psychiatric setting.

AIMS

This study was to collect data to investigate and compare the different drugs for sedation previously used and their effect. This audit aimed to identify the sedation practices prior to the planned randomised controlled drug verses drug trial. The goal was to investigate the types of drugs, the frequency single agents used verses drug combinations. Additionally to determine the effectiveness and adverse effects of different drug combinations based on whether the total dose was higher. Lastly to report the frequency of the use of additional sedation.
medications the duration of the time to sedation and additional sedation after the initial drug administered and adverse events was collected.

OUTCOMES AND CONTRIBUTION TO THE THESIS

The doubling the recommended doses was common practise in the PICU and anecdotally this was often based on the degree of aggression displayed and the size of the patient. The study showed that over half of the patients were given larger than recommended doses of medication to treat ABD. These doses consisted of a single agent or a combination of drugs. The use of larger doses was not associated with more rapid time to sedation but was associated with more adverse events. In addition it showed that additional sedation was rarely given even if it was indicated. Despite the high doses and the increase risk associated with large doses the vital signs monitoring following parenteral sedation was rarely recorded. There was evidence of the patient being observed from outside the seclusion room and their activities recorded, but vital signs were not attended in direct relationship with the parenteral medication administered.

The value of this study is that it provided a snap-shot of current practice in the intensive care unit in the mental health care setting. The prevalence of higher than recommended doses of sedation was not acknowledged by the mental health care setting prior to this study. Yet the common use of high doses were justified by anecdotal evidence that the larger doses achieved faster sedation. An initial review of the medical records of patients sedated for ABD was undertaken prior to the Pre HORD audit found a lack of documentation directly related to the ABD. This included an absence of the effect of the noted, few or no vital signs recording and difficulty establishing adverse effect associated with the sedation. By putting a protocol in place to direct care, investigate effectiveness and monitor vital signs was a positive change of practise. It enabled collection of data and improved the safety of the patient. The results of this study was the baseline for the HORD RCT and the impetus for the establishment of the HNE area guidelines Management of Acute Behavioural Disturbance in HNE Mental Health Units.

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RESEARCH ARTICLE Open Access

A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health unit

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Abstract

Background: Acute behavioural disturbance (ABD) is a common problem in psychiatry and both physical restraint and involuntary parenteral sedation are often required to control patients. Although guidelines are available, clinical practice is often guided by experience and there is little agreement on which drugs should be first-line treatment for rapid tranquilisation. This study aimed to investigate sedation for ABD in an acute mental healthcare unit, including the effectiveness and safety of high dose sedation.

Methods: A prospective study of parenteral sedation for ABD in mental health patients was conducted from July 2010 to June 2011. Drug administration (type, dose, additional doses), time to sedation, vital signs and adverse effects were recorded. High dose parenteral sedation was defined as greater than the equivalent of 10 mg midazolam, droperidol or haloperidol (alone or in combination), compared to patients receiving 10 mg or less (normal dose). Effective sedation was defined as a fall in the sedation assessment tool score by two or a score of zero or less. Outcomes included frequency of adverse drug effects, time to sedation/tranquilisation and use of additional sedation.

Results: Parenteral sedation was given in 171 cases. A single drug was given in 96 (56%), including droperidol (74), midazolam (19) and haloperidol (3). Effective sedation occurred in 157 patients (92%), and the median time to sedation was 20 min (Range: 5 to 100 min). The median time to sedation for 93 patients receiving high dose sedation was 20 min (5-90 min) compared to 20 min (5-100 min; p = 0.92) for 78 patients receiving normal dose sedation. Adverse effects occurred in 16 patients (9%); hypotension (14), oxygen desaturation (1), hypotension and oxygen desaturation (1). There were more adverse effects in the high dose sedation group compared to the normal dose group [11/93 (12%) vs. 5/78 (6%); p = 0.3]. Additional sedation was given in 9 of 171 patients (5%), seven in the high dose and two in the normal dose groups.

Conclusions: Large initial doses of sedative drugs were used for ABD in just over half of cases and additional sedation was uncommon. High dose sedation did not result in more rapid or effective sedation but was associated with more adverse effects.

Keywords: Violence, Sedation, Acute psychiatric unit, Droperidol, Benzodiazepine, Antipsychotic

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Background

Acute behavioural disturbance (ABD) is a common occurrence in the healthcare setting of acute psychiatry [1,2]. Both physical restraint and involuntary parenteral sedation are often required to control patients with ABD. The overall goal is to achieve rapid sedation or tranquilisation to prevent injury to the patient, other patients or staff, whilst minimizing adverse drug effects. When all other strategies such as verbal de-escalation have failed to manage the ABD, parenteral sedation is recommended to prevent distress and reduce harm [3-5].

Although many prescriptive guidelines are available, clinical practice is often primarily guided by experience as there is little agreement on which drugs should be used as first-line treatment for rapid tranquilisation. There is general consensus in the literature that benzodiazepines alone, an antipsychotic alone or a combination of the two are the first line agents for sedation in patients with ABD [1]. Clinical practice guidelines are reasonably consistent in recommending doses of 5 mg to 10 mg of a typical antipsychotic and 5 to 10 mg of midazolam or diazepam (or 2 mg of lorazepam) when used in combination [1,6-9]. However, larger doses are often used, exceeding doses recommended in many clinical practice guidelines [1,9] and the recommendations of the British National Formulary [10]. This is acknowledged by expert clinical opinion [1,11,12].

This study aimed to investigate the types, doses and frequency of drugs used for sedation of ABD in an acute mental health unit, and the frequency of adverse drug effects. We hypothesized that larger doses of sedation might increase the frequency of adverse effects and may reduce the requirement for additional sedation.

Methods

This was a prospective observational study of patients with ABD in an acute mental healthcare unit who required parenteral sedation and physical restraint to protect themselves and/or others. We measured the time to sedation, frequency of adverse effects and use of additional sedation.

The study was undertaken from July 2010 to June 2011 in an eight bed acute mental healthcare unit in a tertiary specialist mental health facility with a 90% occupancy rate. Ethics approval was obtained from the local Human Research Ethics Committee. Consent was waived because of the requirement for immediate treatment and patients' lack of decision-making capacity to consent to medical treatment being given as a duty of care.

The study included all patients administered parenteral sedation for ABD in the acute mental healthcare unit. Admissions to the unit are from the psychiatric emergency care center and are referred from general practitioners, regional hospitals or other units within the institution.

All patients with ABD in the acute mental healthcare unit who did not calm with verbal de-escalation or oral medication and who required physical restraint and parenteral sedation were included. The choice of drug or drugs and the doses administered were determined by the treating clinician. Parenteral sedation was given by initially physically restraining the patient to administer the medications. The patient was then put in a seclusion room and was not mechanically restrained. All patients were involuntary admissions.

Vital signs were recorded every 10 minutes for the first hour then half hourly until the patient settled. A number of the observations were recorded remotely, including the respiratory rate and the level of agitation. Remote observations were commenced from the onset of the ABD until it was considered safe to approach the patient and record vital signs including heart rate, blood pressure, oxygen saturation and respiratory rate. The level of sedation and agitation was recorded using the sedation assessment tool (SAT; Table 1) [13]. The SAT scores the patient from +3 (physically violent) to -3 (unconscious) and allows rapid assessment before and after sedative medication is given. A initial score of +2 or +3 was required and almost always reported in patients requiring physical restraint and parental sedation. We have previously defined effective rapid sedation or tranquilisation as a fall in the score by two levels or a score of zero or less [13-15]. An additional dose of sedative medication was encouraged by the senior medical staff after 30 minutes if there was no response to the first drug given. If the patient did not sedate after 120 minutes they were considered to have failed sedation. The patient was observed for extrapyramidal side-effects and any additional medications were recorded.

At the commencement of the study a previously developed ABD chart was introduced into the acute mental healthcare unit. The ABD chart is part of the medical record and is used to record the level of agitation and sedation with the SAT, vital signs and any adverse effects that occur. The use of the form allowed the simultaneous use

Table 1 Sedation Assessment Tool: SAT

SCORE	RESPONSIVENESS	SPEECH
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious and restless	Normal
0	Responds easily to name, speaks in normal tone	Normal
-1	Responds only if name is called loudly	Slurring or prominent slowing
-2	Physical stimulation	Few recognisable words
-3	No response to stimulation	Nil

of the information for research which was obtained for clinical care of the patient. The following data were then extracted from the ABD chart and medical record: age, sex, medication used including time of administration, dose and additional sedation given. For this study high dose parenteral sedation was defined as a dose greater than the equivalent of 10 mg of midazolam, 10 mg of droperidol or 10 mg of haloperidol, whether as a single agent or a combination of these three drugs. This was based on a controlled trial that compared droperidol (10 mg) versus midazolam (10 mg), versus the combination of droperidol (5 mg) and midazolam (5 mg) [14], and the fact that these were the commonest drugs used in the institution during the study. Patients receiving equal to or less than 10 mg of these three drugs were classified as the normal dose group.

The outcomes for this study were the time to sedation/tranquilisation defined as a fall in the SAT score by two levels or a score of zero or less; the proportion of patients with adverse drug effects defined as a respiratory rate less than 12 breaths per min, systolic blood pressure less than 90 mmHg, oxygen saturation less than 90% or the presence of extrapyramidal side-effects; and the use of additional sedation. The outcomes were compared between patients receiving high dose parenteral sedation and those receiving normal or a lower dose.

Medians and interquartile ranges (IQR) are reported for all continuous variables. Percentages are reported for dichotomous outcomes with 95% confidence intervals (CI). Dichotomous outcomes were compared using Fisher's exact test. All analyses and graphics were done in GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

Results

There were 171 occasions of patients with ABD requiring parenteral sedation in 95 patients during the 12 month period. The median age of the patients was 40 years (15 to 80 yr) and 121 patients were male. The median SAT score prior to sedation was 2 (IQR: 2 to 3). A single drug was administered on 97 occasions and was most commonly droperidol (74; median dose 10 mg; range 5 to 30 mg), then midazolam (19; median dose 10 mg; range 5 to 15 mg) and haloperidol (3; all 10 mg). Combinations of drugs were used in the remaining 75 occasions with the combination of droperidol (10 mg) and midazolam (10 mg) being the most common on 61 occasions. Table 2 lists the different combinations of drugs, the range of drug doses and the frequency used. Ninety three patients (54%) were given more than the equivalent of 10 mg droperidol/midazolam (high dose parenteral sedation), and the majority of these were patients were given 10 mg of either droperidol or haloperidol in combination with 10 mg of midazolam (Table 2). There was no significant difference in age, sex and initial SAT score between patients receiving high dose sedation versus normal sedation dose.

Effective sedation was achieved in 157 patients, and the median time to sedation was 20 min (IQR: 15 to 35 min; Range: 5 to 100 min). The median time to sedation for high dose sedation was 20 minutes (IQR: 18 to 35 min; Range: 5 to 100 min), and 20 minutes (IQR: 11 to 40 min; Range: 5 to 90 min) for normal dose sedation (Figure 1). The remaining 14 patients were not sedated with the initial dose of sedation; eight given high dose and six given normal dose.

Adverse effects occurred in 16 patients (9%), including hypotension (14), oxygen de-saturation (1), hypotension and oxygen de-saturation (1) (Table 2). The frequency of adverse effects was higher for the high dose group compared to the normal dose group [11/93 (12%) vs. 5/78 (6%); p = 0.3] (Figure 2). Of the 14 patients not sedated none received additional sedation. Additional sedation was administered to 9 of the 171 patients (5%), seven in the high dose group and two in the normal dose group.

Table 2 Details of the initial drug type and dose for all 171 episodes and the adverse effects and median time to sedation for each drug type/combination

Drug type	Initial drug	Dose range (mg)	Adverse effects N = 16	Median time to sedation (min)
Droperidol	74	5 to 30	Hypotension (3)	20
Midazolam	19	5 to 15	Hypotension (1)	20
Haloperidol	3	10	0	30
Midazolam + droperidol	61	5 to 15 +	Hypotension (8)	25
		5 to 25	Desaturation/hypotension (1)	
Midazolam + haloperidol	12	5 to 10 + 10	Hypotension (2)	10
			Desaturation (1)	
Droperidol/lorazepam	1	2.5 + 2	0	15
Lorazepam	1	2		40

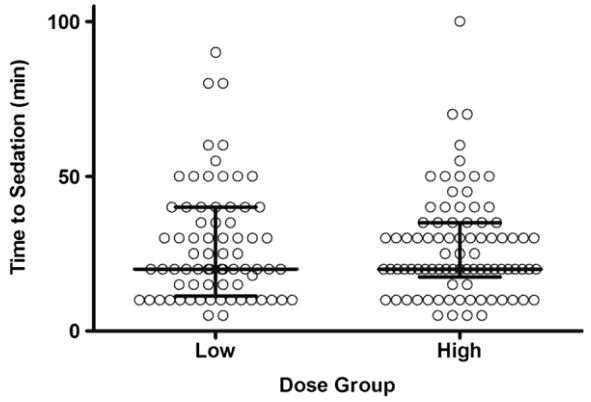

Figure 1 The time to sedation for the high dose group compared to the low dose group.

Discussion

The study found that large initial doses of parenteral sedation are commonly used in the treatment of ABD in the acute mental health setting. The higher dose parenteral sedation was not associated with a shorter time to sedation, but was associated with a higher frequency of adverse effects. Of the 16 adverse drug effects that occurred, almost two-thirds occurred in the patients who received high dose parenteral sedation. The study also showed that the additional sedation was rarely used in both groups.

The high dose parenteral sedation of greater than 10 mg of droperidol, haloperidol or midazolam alone or in combination, is more than the recommended dose in clinical practice guidelines [1,9]. It is also greater than the doses from randomized controlled trials in the acute psychiatric setting where initial doses ranged from 5 to 10 mg of droperidol or midazolam/haloperidol or equivalent amounts of other sedative drugs [16-19].

Unfortunately there is a lack of good evidence to support the effectiveness and safety of drugs used for rapid tranquilisaton of ABD in the acute psychiatry setting. This may be in part due to the difficulties in obtaining ethics approval to study this vulnerable patient population and the need to obtain consent from patients without the capacity to consent. Many trials only include patients with written consent [20,21] and require co-operation from the patients prior to recruitment in the form of performing tests and obtaining blood samples [21] which is rarely possible due to safety issues in patients with ABD. This means that trials in the mental health setting rarely include the most agitated patients and the treatment of this difficult group of patients with ABD is often guided by clinical experience rather than evidence from clinical trials. This may explain the disparity between what is in clinical guidelines based on the literature and what actually happens with the sedation of ABD in the clinical setting.

A difference found in this study compared to other studies of management of ABD in mental health [16-22] was the large initial doses of medication administered to patients, which was often a combination of medications. Combinations of medications, most commonly a benzodiazepine and an antipsychotic, reflects a common strategy in the acute psychiatry setting [6,23]. Although the literature supports the strategy of combining agents, it recommends that lower doses of each medication are used to reduce the risk of adverse effects [6,23]. However, in this study the use of combinations of drugs resulted in a larger total dose being administered in most patients. Importantly, the larger dose did not result in more rapid sedation, but did result in an increased frequency of adverse effects (Figure 2).

The frequency of adverse effects in this study may be an underestimate of the true frequency because of the difficulties in obtaining a complete set of vital signs in these dangerous patients. The inability to have immediate access to the patient due to the level of agitation makes the recording of vital signs and the detection of adverse effects more difficult in the mental health care

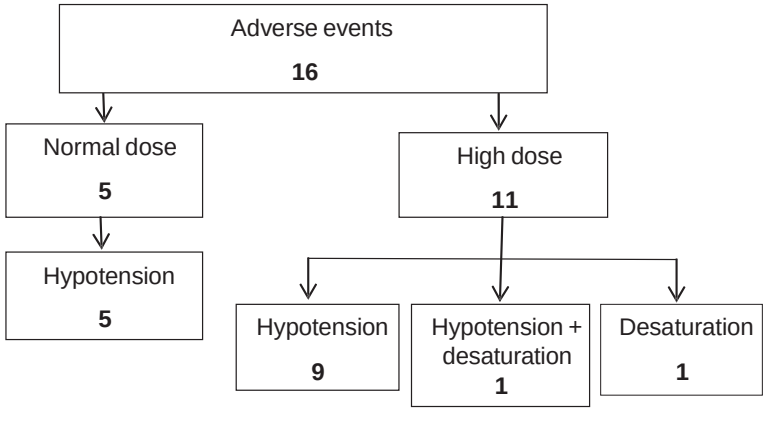

Figure 2 Adverse effects based on high or normal dose sedation and the types of adverse effects.

setting. Only the respiratory rate and SAT could be recorded from outside the seclusion room until the patient was sedated sufficiently to allow the recording of blood pressure and oxygen saturations.

Additional sedation was rarely used in this study which is most likely due to the danger associated with approaching a violent patient on a second occasion once they are in seclusion. In this study 14 patients were not sedated after the initial dose, but additional sedation was only administered in nine patients. This differs to studies of sedation of ABD in the emergency department where 26% to 45% of patients are given additional sedation [14,24].

There were a number of limitations to the study including the non-randomised nature of the sample. This may have introduced bias because patients with more severe ABD may have been more likely to be given high dose sedation. However, there was no difference in the initial SAT score between patients in the high and normal dose sedation groups. The overall frequency of adverse effects in the study was low so the difference between the high and normal dose groups did not reach statistical significance. A larger study is required to confirm this finding.

Conclusion

The study has shown that large initial doses of sedative drugs were used in just over half of cases of ABD in the mental health setting. High dose sedation did not result in more rapid or effective sedation than normal or lower doses of sedation. However, high dose sedation was associated with more adverse effects. Additional sedation was uncommon in all patients. This suggests there is no benefit and potential risk if large initial doses of sedation are given to patients with ABD. Doses recommended by the majority of guidelines should be used and larger doses of single agents or combinations of drugs should be avoided.

Abbreviations

ABD: Acute behavioural disturbance; SAT: Sedation assessment tool; IQR: Interquartile range; CI: Confidence interval.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LC conceived the study, coordinated data collection and drafted the manuscript; VD participated in the design of the study and recruited patients. GI helped conceive the study, designed the study, performed the statistical analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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Chapter 7: Randomised controlled trial of sedationfor acute behavioural disturbance in the psychiatric setting: Haloperidol OR Droperidol (HORD)

BACKGROUND

Aggressive behaviour related to acute psychosis is an ever present problem in emergency admissions to psychiatric wards and intensive care units. It can lead to patient harm and prolonged distress, injury to staff and/or other patients and damage to hospital property if the situation is not rapidly controlled. Intramuscular sedation is commonly used to manage these patients when all other attempts including verbal de-escalation and oral sedation have failed. The most commonly used drugs for this purpose have been benzodiazepines and antipsychotics given by the intramuscular route, mainly midazolam and haloperidol.

Intramuscular midazolam has proven to be unpredictable and can lead to both over-or under sedation of the acutely disturbed patient[1]. It has a significant adverse effect profile due to over-sedation with respiratory depression and/or loss of airways patency[2]. Conversely it is associated with under sedation when used to sedate patients with benzodiazepine tolerance[3]. For this reason we no longer recommend the use of intramuscular midazolam for rapid sedation of acute behavioural disturbance in the emergency department. Haloperidol is also commonly used in this patient cohort but is associated with a high risk of extrapyramidal side effects and a risk of QT prolongation with associated Torsades de Pointes. Droperidol is less commonly used but is a highly sedative antipsychotic medication that is rarely associated with complications[4]. This study aimed to compare the effectiveness of droperidol compared to haloperidol for the sedation of aggressive patients with acute functional psychotic symptoms in a randomised controlled trial. The study was designed to assess both the speed of onset, effectiveness, and adverse effect profile of both agents.

AIMS

This study aimed to compare the effectiveness of intramuscular droperidol to intramuscular haloperidol for sedation of aggressive patients with acute behavioural disturbance based on the time until sedation occurs and the requirements for additional sedation. Additionally we investigated the safety of intramuscular droperidol compared to haloperidol.

The specific hypotheses of the study were:

1. The time to sedation with intramuscular droperidol is shorter than intramuscular haloperidol;
2. Initial sedation with droperidol will require less additional sedation attempts compared to haloperidol;
3. Droperidol will result in a smaller proportion of extrapyramidal side-effects compared to haloperidol;

METHODS

We introduced a blinded randomised controlled trial comparing 10mg intramuscular droperidol to 10mg intramuscular haloperidol in patients with acute behavioural disturbance in the PICU. The primary outcome was the time until the patient is sedated which is measured by a drop in the Sedation Assessment Tool (SAT) by 2 levels or when the patient is scored at zero. The data collected was the patient

demographics and use of additional sedation and frequency of adverse drug effects. A single data sheet the Acute Behavioural Disturbance Chart previously used in the Pre HORD study was used to record all information. The patient was observed in the specifically designed seclusion room or within their bedroom space and had continuous remote monitoring. Distance observations of respiration and level of agitation was initially recorded until it is deemed safe to enter the seclusion room. The 7-point Sedation Assessment Tool (SAT) was used to measure the level of sedation of the patient.

OUTCOMES AND CONTRIBUTION TO THE THESIS

The results from the trial showed no significant difference in time to sedation or frequency of adverse events. The need to challenge the guidelines with evidence based results was necessary and it did not establish the superiority of one drug over another in the mental health setting. This enabled droperidol to be included in the area health guideline. The number of patients who fulfilled the inclusion criteria and were not included in the study was large. These patients predominantly received droperidol 10mg or a lesser dose than 10 mg. Now based on experience with supporting evidence clinicians preference remains droperidol currently. The local guidelines now reflect this practice (See appendix 2).

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Droperidol *v.* haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial

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BJPsych

Droperidol *v.* haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial

Leonie Calver, Vincent Drinkwater, Rahul Gupta, Colin B. Page and Geoffrey K. Isbister

Background
Agitation and aggression are significant problems in acute psychiatric units. There is little consensus on which drug is most effective and safest for sedation of these patients.

Aims
To compare the effectiveness and safety of haloperidol *v.* droperidol for patients with agitation and aggression.

Method
In a masked, randomised controlled trial (ACTRN12611000565943) intramuscular droperidol (10 mg) was compared with intramuscular haloperidol (10 mg) for adult patients with acute behavioural disturbance in a psychiatric intensive care unit. The primary outcome was time to sedation within 120 min. Secondary outcomes were use of additional sedation, adverse events and staff injuries.

Results
From 584 patients, 110 were randomised to haloperidol and 118 to droperidol. Effective sedation occurred in 210 (92%) patients within 120 min. There was no significant difference in median time to sedation: 20 min (interquartile range 15–30, range 10–75) for haloperidol *v.* 25 min (IQR 15–30, range 10–115) for droperidol (P=0.89). Additional sedation was used more often with haloperidol (13% *v.* 5%, P=0.06), but adverse effects were less common with haloperidol (1% *v.* 5%, P=0.12). There were 8 staff injuries.

Conclusions
Both haloperidol and droperidol were effective for sedation of patients with acute behavioural disturbance.

Declaration of interest
None.

Acute behavioural disturbance including verbal aggression and violence is a common occurrence in acute mental health units, with the majority of cases resulting from acute psychosis or substance misuse.[1,2] Most patients settle with verbal de-escalation or agree to take oral medication.[2] Such approaches fail in a proportion of patients whose behaviour escalates from verbal abuse to physical violence. These people often require physical restraint and involuntary parenteral sedation, to prevent harm to other patients, staff and property. The aim in these cases is for the patient to be rapidly tranquillised or sedated.[2,3] Despite the extent of the problem there is little consensus on the most effective and safest drugs for sedation, and there is limited evidence.[4] Clinical practice is generally guided by individual or institutional experience. Guidelines recommend an antipsychotic or benzodiazepine as a single agent or in combination, or an antipsychotic with promethazine.[2,5,6] Common choices are haloperidol alone; haloperidol and lorazepam; haloperidol with promethazine; or a newer antipsychotic such as olanzapine.[3,5,7] Droperidol has been used less commonly after a Food and Drug Administration (FDA) boxed warning in 2002, but recently has been shown to be effective and safe in studies in emergency departments.[8,9] Benzodiazepines are problematic in non-critical care settings because they may cause respiratory depression, and a recent systematic review found that adding a benzodiazepine to haloperidol afforded no benefit but carried the risk of harm.[4] The same review concluded that independent trials with simple outcomes are required to improve the evidence for rapid tranquillisation, because there are significant risks associated with many recommended drugs.[4] We aimed to compare the effectiveness and safety of droperidol with haloperidol for the sedation of patients with acute behavioural disturbance in an acute mental health unit.

Method

We undertook a masked, randomised controlled study of intramuscular haloperidol (10 mg) *v.* intramuscular droperidol (10 mg) for the rapid tranquillisation of patients with acute behavioural disturbance in a psychiatric intensive care unit. The primary outcome was the time to sedation. The study was undertaken from August 2011 to June 2013 in the psychiatric intensive care unit of a large tertiary specialist mental health facility in Australia. The psychiatric emergency care centre of this facility receives over 4400 presentations per year. Patients are generally referred from general practitioners, regional hospitals, other units within the institution or from the community – usually by the community mental health teams or the ambulance or police service. Ethical approval was obtained from the local human research ethics committee. Consent was waived because of patients' lack of decision-making capacity to consent to medical treatment as duty of care. The trial was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12611000565943).

Study participants

All patients with agitation or aggression who were admitted involuntarily to the psychiatric intensive care unit from the psychiatric emergency care centre were eligible for inclusion in the study. They were managed according to a standardised sedation protocol including the use of a purpose-designed acute behavioural disturbance chart. Participants were all adults (418 years of age) with acute behavioural disturbance who required parenteral medication for sedation and in whom verbal

de-escalation and/or oral medication had failed. We excluded patients willing to take oral medication for sedation without physical restraint or seclusion and patients under 18 years old.

Interventions

Patients were identified for the study from either the psychiatric emergency care centre or the in-patient psychiatric intensive care unit. Once patients were recruited to the study they were escorted to the psychiatric intensive care unit and physically restrained with the assistance of security staff to allow the administration of intramuscular medication to the gluteal region. Patients were then either taken to their own room or placed in a seclusion room. They were not physically restrained once the medication had been administered. There was access to resuscitation equipment at all times, and staff had regular training in basic cardiopulmonary resuscitation. The psychiatric intensive care unit is staffed with four nurses for eight patients during daylight hours and the evening, and three nurses overnight. A psychiatrist and a psychiatric registrar are on site in working hours, and a medical officer is available in the hospital after hours.

Pre-packed treatment kits were available in the psychiatric intensive care unit; these had been produced by the Calvary Mater Newcastle pharmacy in conjunction with Richard Stenlake Compounding Chemist, Sydney, Australia. Each kit contained either droperidol (10 mg in 2 ml) or haloperidol (10 mg in 2 ml). Droperidol was purchased from Phebra Ltd (Sydney, Australia); the haloperidol was purchased from Fagron Ltd (Sydney, Australia) and transferred into vials identical to those containing the droperidol formulation. This was done under aseptic conditions by Richard Stenlake Compounding Pharmacy. The 10 mg droperidol dose was based on a similar study in the emergency department and 10 mg of both droperidol and haloperidol are equivalent doses used in rapid tranquillisation in psychiatry.

Block randomisation was used. Microsoft Excel was used to randomly create blocks of four (ABAB, AABB, etc.) or six (ABABAB, AAABBB, etc.). The use of different block sizes meant that it was impossible to predict the next treatment. Each A or B allocation was then assigned a study code. The list of study codes with allocations was generated by a research assistant and supplied to the Calvary Mater Newcastle pharmacy, so that the investigators and treating staff remained unaware of the allocations. The pharmacy relabelled the vials of haloperidol or droperidol with study numbers based on the list of allocations. The vials were then supplied to the psychiatric intensive care unit in sequential order. The psychiatric intensive care unit was kept stocked with treatment kits for the duration of the study. Patients were administered the trial drug and then observed in the seclusion room. Vital signs and the level of agitation and sedation were recorded at 10 min intervals after the trial drug for at least 1 h or until the patient settled. Additional sedation was recommended if the patient showed no sign of settling 30 min after the initial sedation, but this was given at the discretion of the treating physician.

Data collection and processing

A previously developed acute behavioural disturbance chart was introduced into the psychiatric intensive care unit 1 year prior to the trial commencing.[10] During this introductory year the chart was used to record prospectively the level of agitation and sedation in all patients, using the Sedation Assessment Tool (SAT).[11] The SAT (see Appendix) scores the patient from +3 (physically violent) to 73 (unconscious) and allows rapid assessment before and after sedative medication is given. This initial year familiarised the staff with scoring the SAT, developing confidence in its utility and reliability, and ensured that both SAT scores and vital signs were recorded in all patients correctly for the trial.[12] A baseline SAT score was recorded when the patient was recruited to the study; SAT scores and vital signs were then recorded every 10 min after the trial drug for the first hour, then half-hourly until the patient settled. A number of the observations were initially recorded remotely from outside the seclusion room, including respiratory rate and SAT score. Remote observations were commenced from the onset of the acute behavioural disturbance until it was considered safe to approach the patient and record vital signs including heart rate, blood pressure, oxygen saturation and respiratory rate. Adverse events and staff injury were recorded along with any observed extrapyramidal side-effects. Additional medications were given at the discretion of the treating doctors, recorded on the data sheet and charted on the medication chart.

Outcome measures

The primary outcome was the time to sedation, defined as time from the administration of the trial drug until the SAT score decreased by 2 or more or the score was 0 (calm and alert).[11,12] Failed sedation was defined as the patient not being sedated within 120 min. Adverse drug effects were defined as a respiratory rate less than 12 breaths/min, systolic blood pressure less than 90 mmHg, heart rate less than 60 beats/min, oxygen saturation less than 90% or the presence of extrapyramidal side-effects. The use of additional sedation was any medication administered within 60 min of the time of the study drug being given. Successful sedation was defined *post hoc* as patients sedated within 120 min who did not require additional sedation and had no adverse effects.

Statistical analysis

The sample size was calculated to be 230 so as to detect a difference in the time to sedation of 20 min between groups, assuming a within-group standard deviation of 30 min (based on a retrospective audit of psychiatric intensive care unit patients). Because time to sedation was likely to be a non-parametric continuous variable the sample size was calculated using the *t*-test ($a = 0.01$, $b = 0.9$) and 15% added. At the completion of the study one investigator (G.I.) still masked to the allocation audited all primary and secondary outcomes using the original data sheets. Another investigator not involved in recruiting patients or coordination of the study (C.P.) was then given the masked data, and separately the group allocations as either A or B by the pharmacy. At this time only the study labels A or B and not the drug names were known to the investigator. This investigator analysed the data independently and presented this to the other investigators. Only then did the pharmacy reveal whether A or B was haloperidol or droperidol.

Medians, interquartile ranges (IQRs) and ranges are reported for continuous variables. Percentages are reported for dichotomous outcomes with 95% confidence intervals. The continuous primary outcome was analysed using the Mann–Whitney test because the data were non-parametric. Dichotomous secondary outcomes were analysed using a two-tailed Fisher's exact test. A significance level of $P50.05$ was used. All analyses and graphics used GraphPad Prism version 6.02 for Windows (www.graphpad.com).

Results

There were 584 sedation episodes during the 23-month study period and of these 356 were not included in the analysis because the treating clinician elected to give labelled parenteral sedation

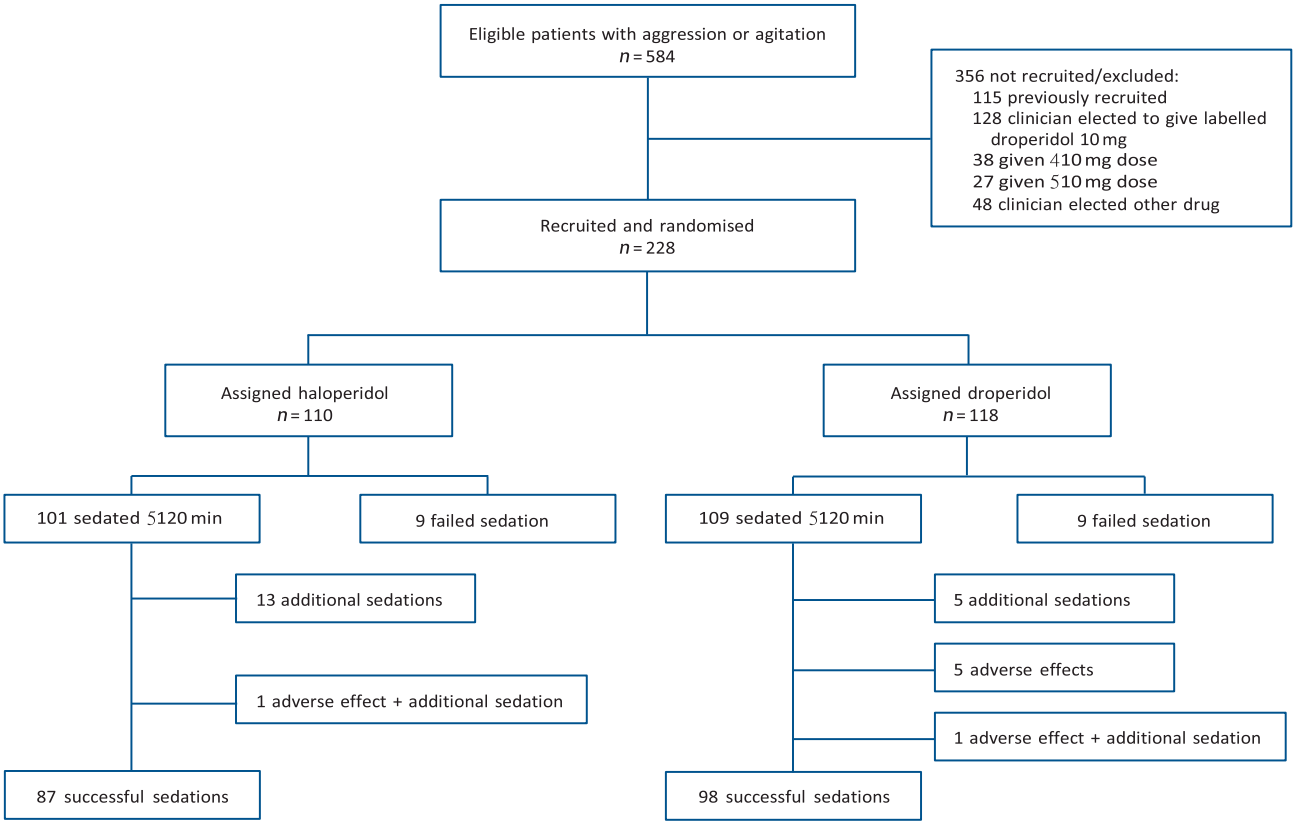

Fig. 1 Patient recruitment and allocation to haloperidol or droperidol.

(most commonly droperidol 10 mg) or a lower or higher dose of labelled parenteral medication, or it was recognised that the patient had already been recruited to the study (Fig. 1). An acute behavioural disturbance chart was filled out for 165 of these 356 episodes (46%), and the baseline characteristics of the patients did not differ from those recruited to the study (Table 1). In 112 of the 356 episodes (31%) an initial SAT score was recorded which was similar to those of the study participants (Table 1).

There were 228 episodes of acute behavioural disturbance in 206 patients recruited to the study, with 5 being sedated on three occasions, 12 on two occasions and 189 on one occasion. In all 228 episodes the patients were randomised: 110 were allocated haloperidol and 118 allocated droperidol. The median age was 33 years (range 16 – 71, IQR 27 – 43) and 144 were male (63%). All were involuntary patients; 114 (50%) had a primary diagnosis of mental illness and 70 (31%) had been admitted with acute behavioural disturbance due to psychostimulant drugs. Baseline SAT scores were +3 in 111 episodes (49%), +2 in 113 episodes (50%), +1 in 3 episodes and not recorded in one. One hundred and ten patients entered into the study needed to be placed in the seclusion room for the protection of themselves and others. Demographic data, cause of acute behavioural disturbance and baseline SAT scores were similar in the treatment groups except that more patients with primary mental illness received haloperidol

Table 1 Baseline characteristics of the patients

	Haloperidol group *n* = 110	Droperidol group *n* = 118	Excluded or not recruited *n* = 356
Age, years: median (IQR)	34 (28–44)	33 (23–42)	38 (28–50)
Gender (male), *n* (%)	69 (63)	75 (64)	192 (54)
Presenting complaint, *n* (%)			
Mental illness	62 (56)	52 (44)	222 (62)
Drug-induced psychosis	30 (27)	40 (34)	59 (17)
Intoxication	6 (5)	11 (9)	16 (5)
Threatened self-harm	4 (4)	2 (2)	54 (15)
Other/unknown	6 (5)	13 (11)	
Baseline SAT score, *n* (%)			
+3	50 (45)	61 (52)	77 (50)[a]
+2	56 (51)	57 (48)	72 (47)
+1	3 (3)	0 (0)	5 (3)
Prior sedation, *n* (%)	9 (8)	11 (9)	NA
Midazolam given with trial drug, *n* (%)	2 (2)	7 (6)	NA

IQR, interquartile range; NA, not applicable; SAT, Sedation Assessment Tool.
a. Baseline SAT scores assessed in 154 episodes.

Table 2 Primary and secondary outcomes

	Haloperidol group *n*=110	Droperidol group *n*=118	Excluded or not recruited *n*=356
Time to sedation, min (IQR)	20 (15–30)	25 (15–30)	20 (20–30)
Sedated within 120 min, *n* (%)	101 (92)	109 (92)	
Additional sedation, *n* (%)	14 (13)	6 (5)	
Adverse effects, *n* (%)			
Hypotension	1 (1)	3 (3)	
Hypotension/desaturation	0 (0)	1 (1)	
Extrapyramidal side-effects	0 (0)	1 (1)	
Oversedation	0 (0)	1 (1)	
Staff injuries, *n* (%)	5 (5)	3 (3)	
Midazolam given with trial drug, *n* (%)	2 (2)	7 (6)	NA

IQR, interquartile range; NA, not applicable.

and more with psychostimulant effects received droperidol (Table 1). In breach of the study protocol midazolam was given nine times simultaneously with the study drug, twice in the haloperidol group and seven times in the droperidol group.

Primary outcome

Effective sedation was achieved in 210 of 228 episodes (92%) with 9 patients receiving haloperidol and 9 patients receiving droperidol not sedating within 120 min (Table 2). The median time to sedation was 20 min (IQR 15 – 30, range 10 – 75) for haloperidol compared with 25 min (IQR 15 – 30, range 10 – 115), which was not statistically significantly different ($P=0.89$) (Figs 2, 3). The median time to sedation in 126 of the 356 episodes not included in the trial was 20 min (IQR 20 – 30, range 10 – 70).

Secondary outcomes

Additional sedation was required in 20 of 228 episodes: 14 (13%) after haloperidol was given and 6 (5%) after droperidol was given (difference 7.6%, 95% CI 0.3 – 15; $P=0.059$). Three of the 18 patients (17%) not sedated were given additional sedation. Adverse effects occurred in seven episodes (3%), one in the haloperidol group and six in the droperidol group: 1 of 110 (1%) *v.* 6 of 118 (5%); $P=0.12$ (see Table 2). Staff injuries resulted from assaults prior to the administration of parenteral sedation and often occurred while the patient was being restrained. There were 44 staff injuries due to acute behavioural disturbance in the psychiatric intensive care unit during the 2-year study period and only eight were recorded on the study data sheets.

Discussion

We found droperidol and haloperidol to be equally effective for the sedation of patients with acute behavioural disturbance in the acute mental health setting. The time to sedation for both drugs was similar and an equal proportion of patients were sedated within 120 min (92%) with a median time to sedation of 20 – 25 min. Although not statistically significant, there were more adverse effects in the patients given droperidol, mainly hypotension, but in no case was treatment required. Conversely, more additional sedation was required in patients given haloperidol, which again was not a statistically significant finding. The study suggests that either haloperidol or droperidol is suitable for the rapid tranquillisation of agitated and aggressive patients in an acute psychiatric unit, half of whom had a primary mental illness.

The most commonly used and recommended drugs for acute behavioural disturbance are benzodiazepines and antipsychotics.[6] A recent study reviewing the current trends in the UK reported lorazepam as the most recommended medication followed by haloperidol, and concluded that multiple agents and combinations are commonly used.[13] In contrast to clinical practice, the systematic review by Powney *et al* found limited evidence to support the use of haloperidol alone, better evidence to support haloperidol with promethazine (to decrease the rate of extrapyramidal side-effects) and no evidence to support the combination of haloperidol and benzodiazepines – and probable harm in the latter combination.[4] In addition, no study has found that other antipsychotics are superior to haloperidol.[4] Our study adds to this and provides further evidence that haloperidol alone is effective and that droperidol is similar and not more effective.

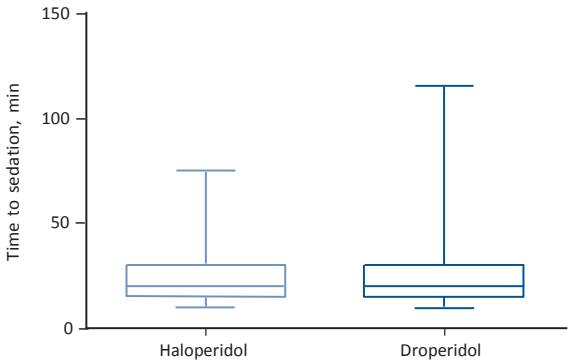

Fig. 2 Time to sedation for intramuscular haloperidol (10 mg) v. droperidol (10 mg).

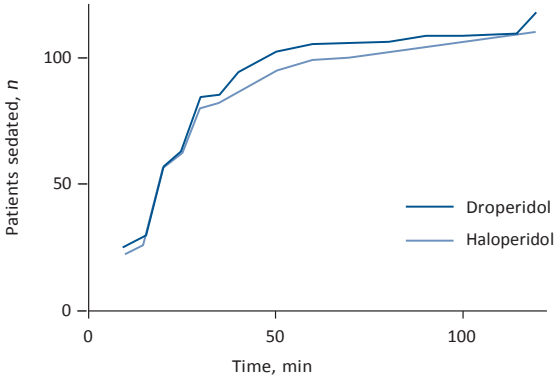

Fig. 3 Cumulative proportion of patients sedated v. time after drug administration

Previous studies

Only two small trials have previously directly compared droperidol with haloperidol, one in the emergency department and one in an acute psychiatric unit.[14,15] Both trials found that intramuscular droperidol required less additional sedation compared with haloperidol, but were small and of low quality.[4,14,15] There has been a resurgence of the use of droperidol in Australia in the past few years owing to its success for sedation of violent and agitated patients in the emergency department.[8,9,16,17] The validity of the 'black box' warning has been questioned by a systematic review,[18] and there are large studies of the safe use of droperidol for sedation prior to the warning.[19] This has, in turn, increased the use of droperidol in some mental health units. Haloperidol has remained the major conventional antipsychotic used to treat undifferentiated acute behavioural disturbance in acute psychiatric units. It has been the most studied antipsychotic and has been used as a comparator in countless trials in mental health.[4] Haloperidol has been shown to be as effective as atypical antipsychotics,[20] but has a higher propensity for extrapyramidal side-effects and has a well-defined association with QT prolongation and torsades de pointes in large doses.[21,22]

There are numerous studies of sedation or tranquillisation of patients with agitation or aggressive behaviour in the mental health setting, but few of these focus on highly agitated and aggressive patients who require physical restraint and parenteral sedation. For such patients rapid sedation rather than 'tranquillisation' is required, which means patients need to be contained within 30 – 60 min. Most studies in the mental health setting have outcomes at 2 h, 4 h, 6 h and 24 h,[23 – 25] which are clearly not appropriate for this type of patient. In contrast, a previous study of haloperidol used a primary outcome of sedation within 20 min and had similar times to sedation to our study.[3] In addition, many other studies exclude intoxicated patients and those with substance misuse,[24,25] making generalising their results to clinical practice difficult because drug and alcohol use and intoxication are common in acute mental health admissions. Our study was restricted to a population of patients with severe agitation and aggression that required parenteral medication, and did not exclude any patient with a drug and alcohol history, making it more applicable to clinical practice.

Undertaking randomised controlled trials in this cohort of patients is difficult for many reasons, not least being the ethical issues surrounding consent for research involving these people. We have demonstrated in Australia that it is possible to undertake a controlled trial of medication without consent in this patient group.[23] The local human research ethics committee agreed parenteral sedation with physical restraint was already being used without patient consent as a duty of care for treatment of these patients. The committee therefore allowed us to waive consent for a study that compared two treatments that were already given as part of standard clinical care. Most controlled trials have required consent for patient recruitment,[24 – 28] which has meant that the trials excluded the majority of severely agitated and violent patients, who were included in our study. Such studies are less useful for defining treatment in patients with severe acute behavioural disturbance, whereas our study provides important evidence about commonly used drugs to inform clinical guidelines for these high-risk and difficult to manage patients.

Adverse events

The large number of staff injuries reported over the study period confirms the severity of the behaviour in these patients. However, all injuries to staff were from assaults prior to parenteral sedation or were sustained in the process of restraining the patient. This suggests that the rapid parenteral sedation of these patients with haloperidol or droperidol prevented further injury to staff. The strict monitoring of adverse effects in this study allowed accurate assessment during the initial period following the onset of sedation. The most common adverse effect was hypotension, which was transient and did not require intervention. Hypotension occurred more commonly with droperidol. It is therefore important that there is routine assessment of blood pressure in patients given droperidol when it is safe to do so. Both droperidol and haloperidol are known to cause extrapyramidal side-effects but in this study there was only one episode of dystonia reported which quickly resolved with oral benztropine.

Limitations

A potential limitation of our study was the number of episodes where patients were not eligible to be recruited, which may have resulted in selection bias. In almost a third of these epsodes the patient was excluded from the study because they had already been recruited. The remaining patients were not recruited because of the clinicians' preference for a particular agent, a different dose of the drugs or a combination of drugs. However, the baseline characteristics of excluded patients were no different from those recruited to the study, including the baseline SAT scores. In addition, the excluded patients had a similar median time to sedation, suggesting that the use of higher doses and combinations was no better than haloperidol or droperidol alone. A major limitation of our study was that extrapyramidal side-effects might have occurred after the 120 min observation period. This is the most likely reason for the low rate of extrapyramidal side-effects reported, because such effects often occur many hours after the drug is administered. Numerous studies of haloperidol *v.* other drugs and/or placebo clearly show that extrapyramidal side-effects are more common with haloperidol.[4] The difference in previous studies is that they were over longer periods and were therefore more likely to report extrapyramidal side-effects.

Finally, the study was not powered to detect differences in the secondary outcomes including adverse effects and additional sedation. Larger studies are now required to determine whether droperidol or haloperidol are associated with a greater risk of adverse effects or requirement for additional sedation.

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Appendix

Sedation Assessment Tool

Score	Responsiveness	Speech
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious/restless	Normal/talkative
0	Awake and calm/cooperative	Speaks normally
71	Asleep but rouses if name is called	Slurring or prominent slowing
72	Responds to physical stimulation	Few recognisable words
73	No response to stimulation	None

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Chapter 8. DORM II Observational Safety and Effectiveness Study

Background:

Violence and acute behavioural disturbance is an increasing problem in emergency departments(ED) and is a difficult and often dangerous management issue that can result in harm to the patient and/or staff. Most of these patients present with an agitated delirium from alcohol intoxication or drug toxicity, including psycho-stimulant abuse. Containment and management of these patients is often done poorly due to the lack of evidence-based guidelines. The decision to sedate a patient who has acute behavioural disturbance is often not simple and involves making an appropriate choice about the particular drug, dose and route of administration. Despite the existence of numerous guidelines for sedation of aggressive patients in the emergency department, there are limited studies on this. We completed a study that suggests initial sedation is best by the intramuscular route(IM) and droperidol appears to be the most effective and safe drug. However there is controversy related to the ED setting often preferring the intravenous route and droperidol's reputation about its potential risk for cardiac arrhythmias. Therefore, further studies are needed to confirm the effectiveness of droperidol and its cardiac safety in a larger cohort in a range of patient populations.

The previous randomized control trial DORM[1] gave us evidence that the use of a standardised IM sedation protocol was simple, more effective and as safe for management of ABD compared to predominantly intravenous sedation.
The DORM study compared the effectiveness of intramuscular droperidol and intramuscular benzodiazepines for sedation of aggressive patients with acute behavioural disturbance in a randomised controlled trial. The value of the DORM project is we have the evidence to support droperidol being a highly sedative antipsychotic medication that is rarely associated with complications and requires less additional sedation to be given.
With the extension of the study to be an observational investigation we aimed to establish the safety of droperidol use in the emergency department in a large sample size in different settings and confirm the validity of a set protocol to care for these difficult to manage patients.
The study was designed to prospectively track the effectiveness of droperidol given by the intramuscular route to calculate the significance of cardiac risk.
It is important to determine if the protocol for recording and monitoring ABD can be implemented into other EDs, both metropolitan and regional. By extending the DORM study to more hospital emergency departments with potentially different patient populations it improved recruitment and provided evidence of its generalisability to other settings.

Droperidol 10mg/2mL concentration: DORM™

In Australia droperidol is only available in the approved concentration of 2.5mg in 1mL under the trade name Droleptan. Therefore to give a dose of 10mg would require a volume of 4mLs to be injected. This would require two intramuscular injections. This is not advisable in a patient who is resisting care. It places the staff at double the risk of having a needle stick injury, and increases the discomfort to the patient in having to be injected twice. A manufacturer of medicines created Droperidol 10mg in 2mL injection and named it after the previous randomised control trial DORM: droperidol or Midazolam. The concentration of droperidol was increased to be the same as Midazolam the comparator drug in the trial to allow for blinding. DORM 10mg in 2mL is an unapproved therapeutic good in Australia. It is manufactured in a Therapeutic Goods Association (TGA) approved pharmaceutical manufacturing facility and is provided under schedule 5A-subregulation 12(1A) of the

TGA and Regulations. The company who manufactures droperidol, Phebra, now supply it at this higher concentration. They intend to submit this product for inclusion in the Australian Register of Therapeutic Goods over the next few years. In the meantime it is available upon a contract signed by each individual institution and Phebra as an agreement to monitor safety and the responsibility of this product remains with the prescriber and the institution. The supply is under a schedule which entails an agreement between the supplier and the institution purchasing the product. DORM™ allows us to give a single injection of 2mL volume 10mg of droperidol the use has spread to other hospitals who are not part of the DORM II safety study. It has been recommended in the clinical practise guideline of Hunter New England Health Mental Health Guidelines and other hospitals include The John Hunter Hospital, Tamworth and The Maitland Hospital. Maitland hospital alone has used over 400 vials of DORM 10mg/2mL.

AIMS

The aim was to investigate the cardiac safety and effectiveness of droperidol for sedation of acute behavioural disturbance in the emergency department setting in order to quash the claims that droperidol causes QT prolongation. The aim was to reinstate droperidol to the role of effective and safe sedation for the treatment of ABD in the emergency department.

Hypothesis:

1. Droperidol when used for rapid sedation does not cause significant lengthening of the cardiac cycle or Torsades des Pointes.

2.Intramuscular droperidol is effective at sedating patients with ABD and a large proportion of patients will respond to the initial dose of droperidol within 15-20 minutes.

3. Droperidol is rarely associated with over-sedation and the requirement for specific interventions for airways compromise

4. Intramuscular droperidol for sedation of patients with ABD is practical and effective and associated with only a small risk of injury or risk to emergency department staff.

METHOD

The study took place in the following emergency departments; Calvary Mater Newcastle, Royal Princess Alexandra Hospital, Prince Of Wales Hospital, The Prince Charles Hospital, Cairns Base Hospital and the Gold Coast Hospital.

When patients present to the emergency department an Acute Behavioural Disturbance chart was used to score the patient using the Sedation Assessment Tool. When the patient met the inclusion criteria and required sedation, they were administered with droperidol as per the treatment regimen. Once recruited the data sheet and ECGs were attended to by the nursing staff and on completion of the study period the information was de-identified and faxed to the national study number.. The ABD chart was used to obtain all baseline demographic information including all primary and secondary outcomes.

The primary outcome is the proportion of patients who have an abnormal QT based on the QT nomogram following the administration of droperidol. The secondary outcomes are the time to sedation and the proportion of patients who have an adverse effect. Additionally we investigated the

requirement for additional parenteral sedation and the requirement for re-sedation and injuries to the patient or staff members

OUTCOMES AND CONTRIBUTION TO THE THESIS

Data was collected from over 1500 patients who were administered with droperidol for ABD. The effectiveness of droperidol is irrefutable with the median time sedation being 20 minutes. This has been consistently repeated over the course of the study[2, 3]. This study is of particular significance and adds value to the body of evidence needed to establish clear guidelines because of the involuntary aspect of the patients recruited which is a true representation of clinical practice.

There no trend for droperidol to QT prolongation and there was no clinical marker for a dose relationship. Most of the cases of QT prolongation were likely due life style choices and co-morbidities. This supports the safety record previously reported by Chase et al[4] with the added advantage of using a measurement method which has been validated and proven to be a more accurate assessment of the risk associated with rate related lengthening of the QT interval[5].

This study was the most significant contribution to the study. It has provided evidence to support the recent clinical practice guidelines for the management of ABD in both the mental healthcare setting and the emergency department setting for the local area health (Appendix 1 and 2).

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The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department

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Study objective: We investigate the safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department (ED).

Methods: This was a prospective observational study in 6 EDs (August 2009 to April 2013). Adult patients requiring parenteral sedation for acute behavioral disturbance received droperidol 10 mg. If this did not sedate the patient within 15 minutes, further sedation was allowed but droperidol 10 mg was recommended as part of a sedation protocol. The primary outcome was the proportion of patients with an abnormal QT interval, defined by the at-risk line on the QT nomogram. Secondary outcomes were effectiveness determined by the time to sedation measured on the Sedation Assessment Tool, use of additional sedation, adverse events, and injury to staff or patients.

Results: There were 1,009 patients with an ECG performed within 2 hours of droperidol administration, with a median dose of 10 mg (interquartile range [IQR]10 to 17.5 mg). Thirteen of the 1,009 patients had an abnormal QT (1.3%; 95% confidence interval 0.7% to 2.3%), but 7 of these had another cause attributed for prolonged QT (methadone, escitalopram, amiodarone, or preexisting). In 1,403 patients sedated with a median total dose of droperidol of 10 mg (IQR 10 to 20 mg), the median time to sedation was 20 minutes (IQR 10 to 30 minutes) and 97% were sedated within 120 minutes. Additional sedation was required for 435 patients (31.0%; 95% confidence interval 28.6% to 33.5%). Adverse events occurred in 70 patients (5%) and oversedation without complications in 109 (8%), the latter more common for patients receiving benzodiazepines as additional sedation (16/109 [15%]). There were no cases of torsades de pointes. Injuries occurred in 34 staff members and 4 patients.

Conclusion: The study supports the use of high-dose droperidol as a safe sedating agent for patients with acute behavioral disturbance in the ED. There is no evidence of increased risk for QT prolongation with the doses used in this study. [Ann Emerg Med. 2015;■:1-9.]

Please see page XX for the Editor's Capsule Summary of this article.

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SEE EDITORIAL, P. ■■■.

INTRODUCTION

Acute behavioral disturbance is a regular occurrence in emergency departments (EDs) worldwide, and it is disruptive and often dangerous for staff and patients. There are numerous causes of acute behavioral disturbance in the ED, the most common being drug and alcohol intoxication, mental illness, and deliberate self-harm.[1] The goal in the management of patients with acute behavioral disturbance is to ensure safety for the patient, staff, and other patients. When verbal de-escalation fails and oral medication is refused or ineffective, parenteral medication is the only option to sedate the patient to enable safe assessment, diagnosis, and treatment. All parenteral medication used for rapid sedation carries inherent risk, and there is little consensus on which drug is optimal. The ideal drug would have a rapid onset and offset, and a low adverse event profile.[2] Benzodiazepines and antipsychotics, as single agents or in combination, have been the 2 major drug groups used for sedating patients with acute behavioral disturbance. The lack of consensus has led to vastly differing clinical practice, with potentially dangerous cumulative doses being administered and high adverse event rates.[3]

Droperidol is a sedating first-generation antipsychotic that has been used to safely treat acute behavioral disturbance for decades.[4,5] A controversial decision was made by the Food and Drug Administration to publish a black box warning for droperidol[6] in December 2001 because of reported cases of QT prolongation and torsades de pointes. The black box warning has led to a marked

Editor's Capsule Summary

What is already known on this topic

Although previously popular, the emergency department (ED) administration of droperidol substantially waned after the Food and Drug Administration issued a controversial black box warning in 2001 about potential QT prolongation.

What question this study addressed

Does high-dose droperidol cause QT prolongation or torsades de pointes?

What this study adds to our knowledge

In this observational study of 1,009 ED adults receiving a median of 10 mg of droperidol for acute behavioral disturbance, QT prolongation was observed in just 1.3%, of whom half had other reasons for such prolongation. There were no cases of torsades de pointes or other serious adverse events.

How this is relevant to clinical practice

Droperidol is safe even with the high doses used in this study.

reduction in the use of droperidol around the world despite a systematic review[7] and increasing evidence that the risk of QT prolongation with droperidol is minimal.[4,8] A number of more recent studies have demonstrated that droperidol is at least as effective as benzodiazepines in sedating patients with acute behavioral disturbance and is potentially safer.[8,9]

Goal of This Investigation

This study aimed to investigate the frequency of QT prolongation and torsades de pointes in patients administered high-dose (10 mg or more) droperidol in the ED for acute behavioral disturbance. In addition, it aimed to investigate the frequency of other adverse events and the effectiveness of droperidol for sedation.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective multicenter observational study of patients administered droperidol for sedation of acute behavioral disturbance in the ED, including the recording of an ECG within 2 hours of drug administration. The study was undertaken in 6 large regional and metropolitan EDs between August 2009 and March 2013. The hospitals ranged in size and case mix and included those in large cities, as well as large urban regional hospitals. Ethics approval was obtained from the Hunter New England Area Health Service Human Research Ethics Committee to cover 2 hospital sites in New South Wales and from the Princess Alexandra Human Research Ethics Committee to cover 4 hospitals in Queensland. Consent was waived because of the requirement for immediate treatment and patients' inability to consent to a study because medical treatment was being given as a duty of care without consent. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12611000031965). Data collection commenced immediately after the completion of a randomized controlled trial of droperidol (the Droperidol or Midazolam [DORM] study) in one of the participating hospitals.[8]

Selection of Participants

ED patients were eligible to be included if they had acute behavioral disturbance, were at risk to themselves or others, and had a score of 2 to 3 on the Sedation Assessment Tool (Figure E1, available online at http://www.annemergmed.com).[10] The Sedation Assessment Tool score is used routinely in all the study EDs to assess the degree of agitation and depth of sedation, with a score of 3 (physically violent) to –3 (unconscious). Patients were excluded if they were willing to receive oral medication for sedation or were younger than 18 years. Inclusion of patients was determined by the ED staff, and in some cases patients scored only 1 on the Sedation Assessment Tool score but required parenteral sedation to prevent their leaving or to have appropriate medical investigation and treatment as a duty of care.

Interventions

A protocol was introduced into each ED for the sedation of patients with acute behavioral disturbance that included the administration of high-dose droperidol (10 to 20 mg) and the use of the Sedation Assessment Tool to determine the effectiveness and safety of sedation (Figure E2, available online at http://www.annemergmed.com). The 10-mg initial dose was based on a previous randomized controlled trial.[8] Patients with acute behavioral disturbance meeting the inclusion criteria were physically restrained and administered 10 mg of droperidol either intramuscularly in the thigh or deltoid muscle or intravenously if a cannula had previously been inserted. If the patient did not settle (ie, Sedation Assessment Tool score decreased by 2 or returned to zero) within 15 minutes, an additional dose of droperidol 10 mg was recommended. After 20 mg of

droperidol had been administered, additional droperidol or other medications were given at the discretion of the treating physicians. Droperidol was available in vials of 10 mg/2 mL concentration (DORM), which enabled 10 mg to be given with a single injection. This formulation of droperidol (DORM) was manufactured (Phebra Pty Ltd, Sydney, New South Wales, Australia) in a pharmaceutical manufacturing facility approved by the Therapeutic Goods Administration in Australia and was provided under schedule 5A-subregulation 12(1A) of the Therapeutic Goods Act and Regulation, Australia. This was an observational study of a clinical protocol in which droperidol was administered, and not a clinical trial, so the use of droperidol was according to the schedule 5A, which relates to clinical use of drugs, and a clinical trials notification was therefore not required.

All patients were initially treated in a critical care area of the ED. They were attached to a cardiac monitor, pulse oximetry, and noninvasive blood pressure machine as soon as they were settled enough. Sedation Assessment Tool scores and vital signs were recorded every 5 minutes from the initial or subsequent doses of droperidol for 20 minutes and then half-hourly. Vital signs, including heart rate (HR), blood pressure, oxygen saturation, and respiratory rate, were ticked on the acute behavioral disturbance data sheet to indicate they were within normal range or recorded numerically if they were abnormal. ECGs were obtained as soon as practical after the patient was sufficiently settled and compliant.

Data Collection and Processing

All data were recorded on a purpose-designed acute behavioral disturbance observation form (Figure E2, available online at http://www.annemergmed.com), which was part of the medical record and used for research data collection. All acute behavioral disturbance data forms and ECGs were de-identified and then faxed to a confidential fax number from each hospital to the chief investigator (L.C.) at the lead site. The acute behavioral disturbance data forms contained demographic information (age and sex), reason for ED presentation, details of drug administration (time and dose), sedation scores, vital signs (HR, blood pressure, oxygen saturation, and respiratory rate), any adverse events, and staff injuries. Data were extracted from the acute behavioral disturbance forms and entered into a relational database (Microsoft Access; Microsoft, Redmond, WA).

ECGs were included only if they were conducted within 2 hours of droperidol administration. The QT interval was manually measured on each ECG with a previously developed method.[11,12] In brief, the QT was measured manually in 3 limb leads and 3 chest leads and the median was taken. HR was taken from the ECG. All ECGs were read by 1 investigator (L.C.), and, to ensure good agreement, a subset of 100 was reviewed by another investigator (C.B.P.), with 86% within 20 ms of one another and 96% agreement for their being normal or abnormal according to the QT nomogram. ECGs were excluded if the HR was greater than 150 beats/min because the QT is difficult or impossible to measure at extreme HR and in the evaluation of the nomogram the fastest HR for drug-induced torsades de pointes was 146 beats/min.[13] The QT was plotted against the HR on the QT nomogram.[11,13] If it was above the "at-risk line," it was considered abnormal.

The QT nomogram was used in preference to HR correction formulae and a particular QTc cutoff because all HR correction formulae are prone to overcorrecting the QT for fast HRs and undercorrecting it for slow ones.[11,14] This is most problematic for Bazett's correction (QTcB), which is accurate only for HRs between 50 and 70 beats/min. The QT nomogram has been evaluated in a systematic review of cases of drug-induced torsades de pointes versus a control group of overdose patients receiving noncardiotoxic drugs and shown to be more sensitive and specific than Bazett's HR correction, with cutoffs at 440 and 500 ms.[13] The QT nomogram has been used for assessment of the risk of QT prolongation in drug overdose patients.[11,14,15]

Outcome Measures

The primary outcome was the proportion of patients who had an abnormal QT, defined as the QT–HR pair's being above the "at-risk" line on the QT nomogram in a 2-hour period after the last droperidol administration (ie, either after the initial dose if only a single dose was given or after the last additional dose of droperidol). The secondary outcomes were the proportion of patients with torsades de pointes, other adverse events, time to sedation, failed sedation, requirement for additional sedation, oversedation (Sedation Assessment Tool score –3), and staff injuries. The time to sedation was defined as the time from the initial dose of droperidol until the Sedation Assessment Tool score decreased by 2 points or more or the score was zero (awake and calm) (Sedation Assessment Tool; Figure E1, available online at http://www.annemergmed.com). Failed sedation was defined as patients not sedated within 120 minutes (ie, a Sedation Assessment Tool score was not recorded with a reduction of 2 levels or a return to zero). The requirement for additional sedation was defined as any medication administered for the purpose of sedation within 60 minutes of the initial droperidol dose. Adverse drug events were defined as any new-onset arrhythmia including torsades de pointes, oxygen saturation less than

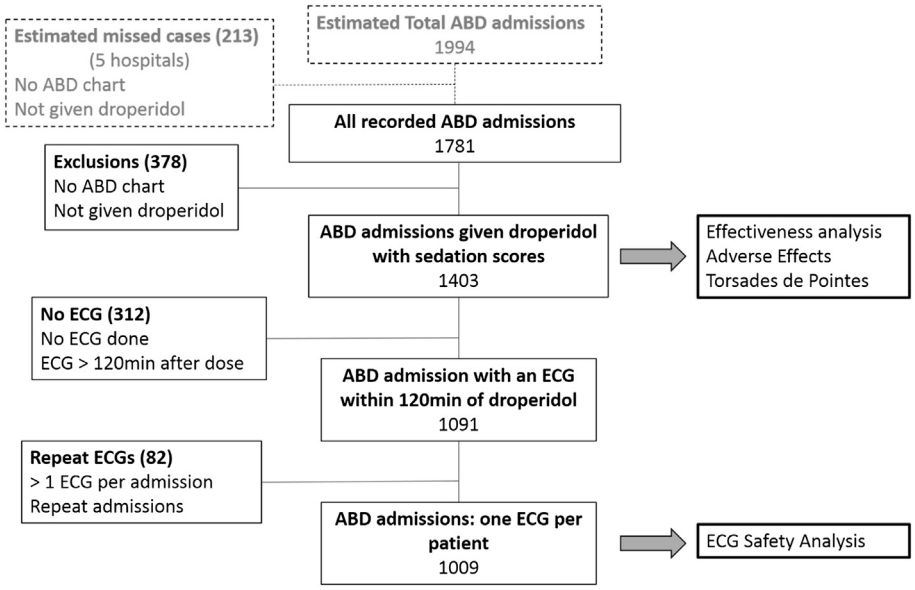

Figure 1. Flow chart of the patients recruited, excluded patients, and the 2 cohorts of patients included in the final analysis. *ABD*, Acute behavioral disturbance; *ECG*, electrocardiogram.

90%, airway obstruction, systolic blood pressure less than 90 mm Hg, and respiratory rate less than 12 breaths/min.

Primary Data Analysis

The sample size for the study was based on demonstrating that the incidence of QT prolongation and torsades de pointes is rare and QT prolongation occurs in no more than 0.5% of patients. Assuming that an abnormal QT does not occur in the study, we would need 950 patients to be confident (97.5% confidence interval [CI]) that an abnormal QT occurs in less than 0.5% of patients. This is calculated as the 95% CI around a proportion of no events in 950 patients (0/950), using the Wilson procedure with continuity correction. We aimed to recruit 1,000 patients, assuming that ECGs might not be conducted in 5% of them.

Medians and interquartile ranges, 95th percentiles, or ranges are reported for continuous variables, and dichotomous variables are reported as percentages with 95% CI, using the Wilson procedure with continuity correction. The primary outcome was presented as a proportion with 95% CI. All analyses and graphics were conducted with GraphPad Prism (version 6.03; GraphPad Software, San Diego, CA).

RESULTS

There were 1,781 patient presentations reported to the investigators from the 6 EDs for acute behavioral disturbance between August 2009 and March 2014, with a median of 164 per hospital (52 to 928). There were 1,403 of 1,781 presentations with a complete set of data collected, including when droperidol was the initial drug given and there was a completed acute behavioral disturbance chart and a time to sedation recorded. There were no cases of torsades de pointes in these excluded patients. In the hospital recruiting the largest number of patients (928 of 1,781 [52%]), there was close to 100% capture of acute behavioral disturbance cases in which parenteral sedation was administered because the security log was reviewed weekly and droperidol use was closely monitored by the pharmacy. In this hospital, only 653 of 928 patients (70%) were included in the sedation cohort compared with a median of 87% (Range: 83% to 91%) in the other 5 hospitals, indicating that there were cases missed at the other hospitals for which no information was faxed. By correcting for the difference between inclusion rates of each hospital compared with that of the first hospital, we estimate that 213 patients were missed at the other sites and not recorded, making the estimated total 1,994 (Figure 1). Review of the excluded cases at the first hospital indicated that staff being too busy to fill out charts and new junior staff preferentially using another drug were the main reasons for exclusion. No cases were excluded where droperidol was given and there was an adverse event, and there were no cases of torsades de pointes.

The cohort of 1,403 patients was used to assess the effectiveness of droperidol for sedation and adverse events. In 1,091 admissions, there was at least 1 ECG conducted within 120 minutes, excluding multiple ECGs and multiple admissions for the same patient, and ECGs with a HR greater than 150 beats/min. From this, there were

Table 1. Baseline characteristics of the 2 cohorts of patients.

	Effectiveness Cohort			QT Cohort		
Demographics/Characteristics	**Number**	**%**	**N=1,403**	**Number**	**%**	**N=1,009**
Age, median (IQR), y	34 (25–44)		1,391	34 (25–43)		999
Men (%)	840	59.9	1,403	631	62.5	1,009
Reason for presentation						
Alcohol intoxication*	609	52.6	1,157	421	50.6	832
Deliberate or threatened self-harm	287	24.8	1,157	200	24.0	832
Psychostimulants	160	13.8	1,157	130	15.6	832
Mental illness/psychosis	182	15.7	1,157	142	17.1	832
Head injury	16	1.4	1,157	12	1.4	832
Medical cause	30	2.6	1,157	10	1.2	832
Other	56	4.8	1,157	25	3.0	832
Blood alcohol level, median (IQR), mg/dL	0.23 (0.18–0.28)		278	0.22 (0.18–0.28)		
Previous sedation†	67	4.8	1,403	49	4.9	1,009
Baseline Sedation Assessment Tool scores						
3	827	61.9	1,335			
2	473	35.4	1,335			
1	35	2.6	1,335			
Initial droperidol dose, median (95th percentile), mg	10 (10–10)			10 (10–10)		

*Patients with alcohol intoxication could also have another reason for presentation.
†Sedation given in the hours before parenteral droperidol, usually before the hospital.

1,009 single patient admissions included in the ECG safety analysis (Figure 1). The HR was greater than 150 beats/min in only 3 patients who were excluded. The demographic details for each cohort are included in Table 1 and were similar among the hospitals.

The median total dose of droperidol given before the first ECG in the 1,009 patients was 10 mg (interquartile range 10 to 17.5 mg). In these 1,009 ECGs from single patients, the median QT was 360 ms (95th percentile 320 to 440 ms). Thirteen of the 1,009 patients had an abnormal QT (1.3%; 95% CI 0.7% to 2.3%), which is shown on the QT nomogram (Figure 2). The number of cases of an abnormal QT for each hospital is included in Table E1, available online at http://www.annemergmed.com. Of the 13 patients with abnormal QTs, 2 had preexisting abnormal QT according to ECGs before or after the administration of droperidol, 2 were receiving methadone, 2 were receiving escitalopram, and 1 was receiving amiodarone, all drugs associated with QT prolongation (Figure 2). Excluding patients with another reason for a prolonged QT interval, there were only 6 patients (0.6%; 95% CI 0.2% to 1.4%) with an abnormal QT. There were no cases of torsades de pointes. There were 33 elderly patients (age ≥65 years; 3.3%) who had a median QT of 390 ms (95th percentiles 320 to 448 ms), which was slightly longer than that of all patients (Table E2, available online at http://www.annemergmed.com).

The median initial dose of droperidol in the 1,403 patients was 10 mg (95th percentile 10 to 10 mg; range 2.5 to 20 mg) and the median total dose was 10 mg (95th percentile 10 to 20 mg; range 2.5 to 40 mg). The median time to sedation in the 1,403 patients was 20 minutes (interquartile range 10 to 30 minutes; range 2 to 120 minutes). There were 1,354 patients (97%) sedated within 120 minutes and 49 patients who failed sedation (Figure 3). The initial dose of droperidol effectively sedated 968 patients (69.0%; 95% CI 66.5% to 71.4%) and

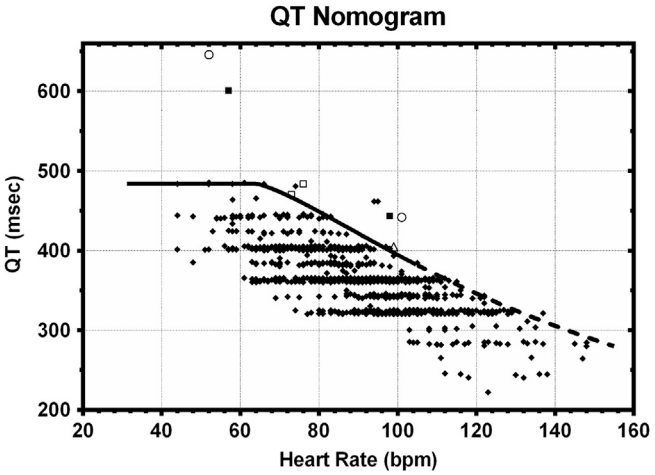

Figure 2. QT nomogram with plots of QT/HR pairs (black filled circles) below and above the "at-risk" line (black line). The QT nomogram is used for determining whether a QT interval is at risk from a single 12-lead ECG (modified from Figure 1 of Fossa et al[21]). The at-risk line is a close approximation of the figure and the dashed section is extrapolated for faster HRs.[13] Two patients had abnormal QT before receiving droperidol (open circles), 2 patients were receiving methadone (filled squares), 2 patients were receiving escitalopram (open squares), and 1 patient was receiving amiodarone (open triangle).

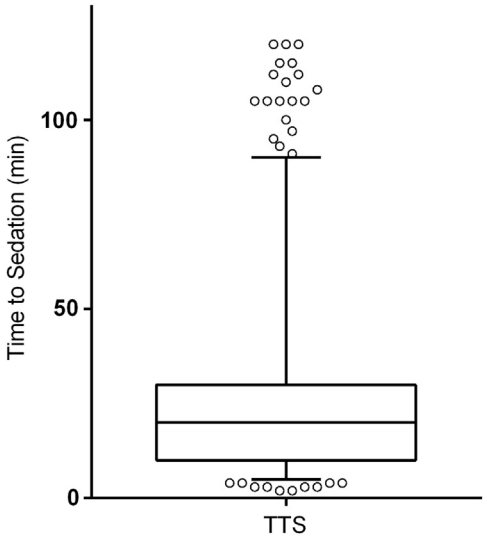

Figure 3. Box-and-whiskers plot of the times of sedation for the 1,354 patients who sedated within 120 minutes. The whiskers are 5th and 95th percentile, the box is interquartile range, and open circles are outliers. The 49 patients not sedated within 120 minutes are not included on the plot but are included in the calculation of the median, percentiles, and ranges. *TTS*, Time to sedation.

additional sedation was required for 435 patients (31.0%; 95% CI 28.6% to 33.5%), although droperidol was not used in all cases of additional sedation. Of these 435 patients, 323 (23.0%) had 1 further dose, 70 (5.0%) 2 further doses, 28 (2.0%) 3 further doses, and 14 (1.0%) 4 or more additional doses. Droperidol alone was given to 299 of the 435 patients who had additional sedation. Additional sedation was used more often for patients given a lower initial dose, 26 of 61 (42.6%; 95% CI 30.3% to 55.9%) given 5 mg compared with 405 of 1,337 (30.3%; 95% CI 27.9% to 32.8%). Only 3 patients were given 2.5 mg as an initial dose, and 2 required additional sedation.

Oversedation (Sedation Assessment Tool score –3, equivalent to U on the AVPU score) occurred in 109 patients (7.8%). Benzodiazepines were given for 16 of the 109 patients (15%) who were oversedated compared with only 82 of 1,294 patients (6.3%) who were not. Table 2 shows that 3 or more additional sedations and the use of benzodiazepines are associated with oversedation. Elderly patients (N=61; 4.3%) had a slightly longer time to sedation (median 25 minutes) and larger requirement for additional sedation (43%) (Table E2, available online at http://www.annemergmed.com).

There were 71 adverse events in 70 patients (70/1,403 [5.0%]; 95% CI 3.9% to 6.3%), with 1 patient having 2 adverse events (airway obstruction and desaturation). The number of each of the adverse events is shown in Table 3, with the commonest being hypotension (28 patients) and desaturation (22 patients). Of the 8 patients with airway obstruction, 6 required a nasopharyngeal airway or jaw thrust briefly, 1 was repositioned on the side, and 1 was intubated but had taken a tricyclic antidepressant overdose. Only 2 of the 8 received 10 mg droperidol alone, 3 received benzodiazepines before droperidol (out-of-hospital), 2 had sedative overdoses, and 1 was given 30 mg droperidol and 200 mg ketamine. Eleven of the 22 patients with desaturation had oxygen applied and 3 were stimulated or had jaw thrust. Table 2 shows that additional sedation or sedation with benzodiazepines was not associated with increased adverse events except oversedation. One patient had a cardiac history and developed atrial flutter that resolved.

There was no difference in the total dose given to patients who had adverse events compared with those who did not. The 98 patients given benzodiazepines (midazolam or diazepam) in addition to droperidol had similar numbers of adverse effects compared to the 1305 given droperidol alone (4/98 [4.1%] versus 66/1305 [5.1%]). Injuries were reported in 38 admissions (2.7%), including 34 staff injuries (punches [13], kicks [4], bites [2], spitting [6], scratches [2], needle stick injury [1], and unknown [6]) and 4 patient injuries. There were 4 adverse events in 61 elderly patients, which was similar to those of all patients (Table E2, available online at http://www.annemergmed.com).

LIMITATIONS

A limitation of the study was the difficulty obtaining ECGs at the same time for every patient, and many ECGs could not be done within the 2-hour timeframe of administration of droperidol. Patients were either uncooperative or staff were reluctant to disturb them once they were settled. However, more than 1,000 ECGs were conducted within 2 hours of droperidol administration, and this is when the peak effects of droperidol are likely to occur. Despite the large number of ECGs, the study was still unable to rule out rare adverse events (<0.1%): torsades de pointes. The rarity of torsades de pointes means that much larger studies are required to show that there is no or minimal association between droperidol and torsades de pointes.

A second limitation of the study was that in only 1 hospital was the data collection completely consecutive. We estimated that approximately 213 patients were missed at the other 5 sites. Although there is a small likelihood of bias being introduced because potentially a proportion of clinicians avoided droperidol, this avoidance did not appear to be based on particular patient characteristics and, when

Table 2. Number of patients given additional sedation, including the number of additional sedations and drugs given, the proportion with adverse events, and the proportion with oversedation.

Drug Given	Number	Adverse Events	%	Oversedation	%
All patients	1,403	70	5.0	109	7.8
Single droperidol dose, mg	968	45	4.6	73	7.5
10	933	43	4.6	72	7.7
5	35	2	5.7	1	2.9
All additional sedation patients	435	25	5.7	36	8.3
Additional sedation, 1 dose	323	18	5.6	25	7.7
Two droperidol doses	280	16	5.7	18	6.4
Droperidol+benzodiazepine	40	2	5.0	7	18
Droperidol+midazolam	33	1	3.0	5	12
Droperidol+diazepam	7	1	14.3	2	29
Droperidol+other (1 add)	3	0	—	0	—
Additional sedation, 2 doses	70	4	5.7	5	7.1
3 droperidol doses	15	0	—	1	6.7
Droperidol+2 other drugs	55	4	7.3	4	7.3
Droperidol (×2)+midazolam	17	2	11.8	1	5.9
Droperidol (×2)+diazepam	8	0	—	2	25
Droperidol (×2)+ketamine	20	1	5.0	0	—
Droperidol (×1)+benzodiazepine (×2)	7	0	—	1	14
Droperidol (×2)+dexmedetomidine	1	1	100	0	—
Droperidol (×2)+other*	2	0	—	0	—
Additional sedation, 3 doses	28	2	7.1	4	14
4 droperidol doses	4	0	—	0	—
Droperidol+3 other drugs	24	2	8.3	4	17
Droperidol (×2)+midazolam (×2)	8	0	—	3	38
Droperidol (×3)+midazolam	3	0	—	0	—
Droperidol (×3)+ketamine	7	1	14	0	—
Other combinations†	6	1	17	1	17
Additional sedation, 4 or more doses	14	1	7.1	2	14
Droperidol+benzodiazepines	7	0	—	1	14
Droperidol+benzodiazepines+dexmedetomidine	4	0	—	1	25
Droperidol (×3)+dexmedetomidine	1	1	100	0	—
Droperidol+ketamine	2	0	—	0	—
Additional sedation includes a benzodiazepine	98	4	4.1	16	15
Additional sedation only droperidol	299	16	5.4	19	6.4
All patients not given a benzodiazepine	1,305	66	5.1	93	7.1

—, No cases.

*One patient was given haloperidol and 1 patient was intubated for agitation/aggression.

†One patient had an adverse event with dexmedetomidine and another had oversedation with zuclopenthixol.

reviewed at one hospital, was mainly because of junior staff unfamiliar with droperidol.

Another limitation was that not all the demographic and baseline data were available for all patients because the information on the acute behavioral disturbance observation form was incomplete in a small number of cases. The investigators relied on the treating team to fill out the form and fax it back. However, state laws required that all information faxed across borders be deidentified, so the investigators were unable to double check this information once patients had been discharged. Less than 5% of the baseline data were missing and this did not affect the study outcomes.

The study was conducted in the setting of the ED with patients who could not be settled with verbal de-escalation or oral sedation. A limitation of this is that the results cannot be generalized to other settings such as the acute psychiatric setting, where mental illness is far more prevalent, or general medical or drug and alcohol withdrawal patients. One recent study in a psychiatric

Table 3. Number of the different adverse events and the proportion in the total cohort.

Adverse Event	No.	%
Desaturation (<90%)	22*	1.6
Airway obstruction	8	0.6
Hypotension	28	2.0
Extrapyramidal adverse events	7	0.5
Arrhythmia	1	0.1
Hypoventilation (respiratory rate <12 breaths/min)	4	0.2
Seizure	1	0.1
No adverse events	1,333	95

*One patient had both airway obstruction and desaturation.

ICU demonstrated that droperidol and haloperidol were safe and equally effective in sedating agitated and aggressive patients.[16] Further studies are required in different patient groups to establish the safety and effectiveness of droperidol.

DISCUSSION

This study has shown that an abnormal QT interval is rare in a large cohort of patients given high-dose droperidol. In addition, there were no cases of torsades de pointes in the larger cohort of 1,403 patients, suggesting that the risk of torsades de pointes is less than 0.3% according to the size of the cohort. In addition, the study showed that droperidol was effective for sedation, with almost all patients being sedated within 120 minutes and less than a third requiring 2 or more doses. Adverse events occurred in 5% of patients, and oversedation with a Sedation Assessment Tool score of –3 occurred in 8% but did not require any specific intervention. Oversedation was more common in patients given additional benzodiazepines and in patients requiring additional sedation on 3 or more occasions. The study demonstrates that high-dose droperidol appears to be relatively safe and effective for sedation of acute behavioral disturbance in the ED. Initial doses of less than 10 mg were associated with the requirement for additional sedation.

The frequency of abnormal QT intervals was 1.3% (95% CI 0.7% to 2.3%), which was not significantly different to that observed in the control group of patients used to evaluate the QT nomogram, 1.3% (95% CI 0.4% to 3.4%).[13] In half of the patients with an abnormal QT, there was another clear cause for it, including known QT-prolonging drugs (eg, methadone) or preexisting QT prolongation. This and the absence of torsades de pointes suggest that droperidol in doses of 10 to 20 mg is highly unlikely to cause QT prolongation and patients do not need routine ECGs after receiving droperidol. This is consistent with results of smaller randomized controlled trials of droperidol, which also did not demonstrate QT prolongation as a problem.[8,9,17]

The goal of effective sedation is rousable sleep, not unconsciousness.[2] In this study, only 109 of the 1,403 patients (7.8%) had a sedation score of –3, and thus greater than 90% were either easily roused or roused to physical stimuli. This had been identified in the previous DORM study, which showed that patients given droperidol were rarely oversedated.[8] Patients who were given midazolam or diazepam as part of their additional sedation were at least twice as likely to develop oversedation (Table 2). This association of benzodiazepines with oversedation has been shown in previous studies.[8,18,19] This supports concerns about the use of benzodiazepines for sedation of patients with acute behavioral disturbance. To our knowledge, no study has shown significant benefit of benzodiazepines over droperidol in the sedation of this patient group.[8,9,19,20] Knott et al[9] reported only a median difference in the time to sedation of 1.5 minutes when midazolam was given intravenously compared with droperidol, and there was no difference between midazolam and droperidol in the DORM study.[8] Oversedation was also associated with 3 or more attempts at additional sedation, although not when droperidol was the only agent used (Table 2). This suggests that sedation with combinations of agents, particularly benzodiazepines, should be avoided.

This study has shown that droperidol is relatively safe and effective for the management of violent and aggressive patients in the ED and that there was no increased risk of QT prolongation and torsades de pointes according to a large cohort of cases. Very large studies are required to completely rule out any risk of QT prolongation and torsades de pointes. The study also supports concerns about the increased oversedation and adverse events associated with the addition of a benzodiazepine to droperidol.

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APPENDIX

Table E1. The number of patients with an abnormal QT for each hospital, including the proportion with 95% CIs.

Hospital	Number of ECGs	Abnormal QT	Proportion, %	95% CI
1	67	0	0	0–6.8
2	389	8	2.10	1.0–4.2
3	35	0	0	0–12.3
4	296	4	1.40	0.4–3.7
5	138	1	0.70	0–4.6
6	84	0	0	0–5.5

Figure E1. Sedation Assessment Tool.

Score	Responsiveness	Speech
3	Combative, violent, out of control	Continual loud outbursts
2	Very anxious and agitated	Loud outbursts
1	Anxious/restless	Normal/talkative
0	Awake and calm/cooperative	Speaks normally
−1	Asleep but rouses if name is called	Slurring or prominent slowing
−2	Responds to physical stimulation	Few recognizable words
−3	No response to stimulation	None

Table E2. Demographics, baseline characteristics, and outcomes for elderly patients (>65 years) compared with the whole cohort.

Demographics/Characteristics	Effectiveness Cohort, Elderly	%, N=61	Effectiveness Cohort, All	%, N=1,403	QT Cohort, Elderly	%, N=33	QT Cohort, All	%, N=1,009
Age, median (range), y	75 (65–93)		34 (25–44)		74 (65–93)		34 (25–43)	
Men, %	43	70	840	60	24	73	631	63
Droperidol dose, median (95% PI), mg	10 (5–10)		10 (10–10)		10 (10–10)		10 (10–10)	
QT, median (95th percentile), ms					390 (320–448)		360 (320–440)	
Time to sedation, median (IQR)	25 (12–37)		19 (10–30)					
Sedated within 120 min	54	89	1,354	97				
Additional sedation, %	26	43	453	32				
Adverse events, %	4	7	71	5				

PI, Percentile.

Chapter 9: CONCLUSION OF SEDATION of ACUTE BEHAVIOUR DISTURBANCE

The pharmacological treatment of patients with acute behavioural disturbance (ABD) is difficult and remains controversial. Clinical practice is often based on anecdote and historical practice, despite numerous studies of drugs over the last two decades. The goal of this thesis was to build on previous studies on drugs for sedating patients with ABD so that better information can be given to healthcare workers to treat their patients. In particular the thesis aimed to expand on the initial randomised control trial of droperidol (DORM) by assessing a standardised sedation protocol in a larger group of ED, including a subgroup of elderly patients, as well as patients in the acute mental health setting. The DORM study suggested that droperidol alone was as effective as midazolam or a combination of droperidol and midazolam, and was potentially safer than midazolam or the combination. The thesis therefore assessed droperidol monotherapy in a number of different studies, including large numbers of patients and different settings.

Overall the thesis has showed that droperidol is a safe agent for the use in patients with ABD in both the ED and the acute mental health settings, including elderly patients. In particular it has demonstrated that QT prolongation is very rare with droperidol and fears about a significant risk of QT prolongation and TdP with droperidol are unfounded. The series of studies also show that droperidol is effective for sedation of patients with ABD, and in the acute mental health setting is similarly effective compared to haloperidol, arguably the most commonly used agent worldwide. The thesis also evaluated a simple way to assess sedation and agitation in this patient group which was then used in all the interventional studies.

We developed a cohort of over 1500 patients who were sedated with droperidol over a four year period with no serious or unexpected drug related adverse events. In addition, the majority of these patients were sedated with one or two doses of droperidol suggesting it is an effective agent for ABD. From this cohort we investigated two subgroups of patient, a small number with holter recordings to assess the effect of droperidol on the QT in more detail and geriatric patients. The study of holter recordings in patients given droperidol provided additional support that droperidol had a minimal effect on the QT using highly accurate measurements of the QT interval at multiple time points after drug administration. There were a small number of patients with prolonged QT intervals, but assessment of the

timing of the changes in the QT and associated drug use suggested that the QT prolongation was not due to droperidol.

The study of geriatric patients (> 65y) highlighted the difficulties with sedation of this vulnerable group and suggested that droperidol was effective and safe. Although only an observational study it suggested that a reduced dose (5mg) initially was appropriate to gauge the sedating effects. However, the majority of patient required a second dose. The study provides the best current evidence that droperidol can be used in this population. .

A pilot study of dexmedetomidine in the ED for sedation of patients with ABD was undertaken to investigate potential drugs for patients who failed sedation after two doses of droperidol. However, the study found that there was a high rate of adverse effects and was too labour intensive in the ED to pursue.

A major part of the thesis was exploring the use of droperidol in the acute mental health settings where haloperidol and midazolam were the most commonly used drugs. There was a concern whether droperidol would be as effective when used in a patient cohort who have had previous exposure to antipsychotics. To make it possible to undertake a trial of droperidol in the Psychiatric Intensive Care Unit the ABD chart was altered to suit the setting and introduced for a period of 12 months. We initially undertook an observational study of the sedation in this setting to familiarise staff to using a standardised assessment chart, investigate the currently used medications and ensure vital sign observations were monitored. This study found that high dose sedation is used in the acute mental health setting where a large initial dose is given and additional sedation is rare.

The randomised controlled trial of haloperidol versus droperidol was then undertaken to investigate the effectiveness and safety of droperidol in this setting compared to the most commonly used agent. The study demonstrated that droperidol and haloperidol were equally effective in this setting but a larger study was required to explore differences in secondary outcomes between the two, including adverse effects and requirement for additional sedation.

The DORM II safety and effectiveness study was an assessement of the full cohort of 1403 ED patients given droperidol for ABD. The study aimed to provide evidence for the cardiacsafety of droperidol because this was the reason for the black box warning which changed the use of droperidol worldwide. The acquisition of over 1000 ECGs with no QT prolongation and no cases of TdP provided significant support for the safety of droperidol for ABD. .

Future studies are required to explore the use of droperidol in other settings such as pre-hospital sedation of violent patients and its use in other hospital settings, such as general medical wards, geriatric inpatient units and drug and alcohol inpatient units.

Results from the thesis have led to changes in clinical practice, including changes in local guidelines for the sedation of patients with ABD in both EDs and in the mental health setting. The local ED now uses a standardised ABD chart which includes the SAT score and highlights to the staff the need for regular assessment of the patient, including regular vital sign monitoring and the need for additional sedation in some cases. In addition a simple re-dosing strategy for droperidol has been evaluated with an initial dose of 10mg and repeating this after 15 minutes if required. The same protocol was also introduced to many other EDs. The results of the thesis also contributed to the development of a practice guideline for Mental Health patients in the local Area Health Service.